STATE UNIVERSITY
NOV 20 1961
LIBRARY

H.C.

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY NOVEMBER 4 1961

RECEIVED
NOV - 1961
HEALTH CENTER

TABLE OF CONTENTS

Prognosis of Intrathoracic Sarcoidosis in England J. G. SCADDING, M.D., F.R.C.P. 1165

The Birmingham Oral Contraceptive Trial P. ECKSTEIN, M.D., J. A. H. WATERHOUSE, PH.D., GLENYS M. BOND, M.R.C.S., L.R.C.P., W. G. MILLS, F.R.C.S., F.R.C.O.G., DOROTHY M. SANDILANDS, M.B., and D. MARGARET SHOTTON, M.B., M.R.C.O.G. 1172

Clinical Trials of Oral Contraceptives ELEANOR MEARS, M.B. 1179

Injuries from Fireworks DOUGLAS JACKSON, M.D., F.R.C.S. 1184

Pulmonary Agenesis H. EVERLEY JONES, M.B., F.R.C.P., and C. H. L. HOWELLS, M.D. 1187

Hypopituitarism Associated with Intracranial Aneurysms W. VAN 'T HOFF, M.B., M.R.C.P., R. W. HORNABROOK, M.D., M.R.A.C.P., and VINCENT MARKS, B.M., M.R.C.P.Ed. 1190

PRELIMINARY COMMUNICATIONS

Production of Calciphylactic Facial, Oesophageal, and Mediastinal Lesions by Combined Treatment with Dihydrotachysterol and Thorium Dioxide. HANS SELYE, M.D., D.SC., F.R.S.C., GIOVANNI GENTILE, M.D., and RENÉ VEILLEUX, D.V. 1194

MEDICAL MEMORANDA

A Case of Extensive Interstitial Calcinosis. C. GARDIKAS, M.D., M.SC., PH.D., and J. HADJIOANNOU, M.D. 1196

Self-induced Fatal Air Embolism in a Man. R. T. COOKE, M.D. 1197

BOOK REVIEWS 1198

CLINICOPATHOLOGICAL CONFERENCE

A Case of Renal Failure 1208

GENERAL ARTICLES AND NEWS

G.P.s and Preventive Medicine 1215

Fifth World Assembly of the Israel Medical Association 1216

To-day's Drugs 1217

MEDICAL SCHOOL OPENINGS 1217

OBITUARY 1227

MEDICAL NOTES IN PARLIAMENT 1229

UNIVERSITIES AND COLLEGES 1230

MEDICAL NEWS 1234

BIRTHS, MARRIAGES, AND DEATHS 1236

QUESTIONS AND COMMENTS 1237

MEDICO-LEGAL

No Appeal Against Finding of Insanity 1230

Burden of Proof in Automatism 1230

LEADING ARTICLES

Management of Attempted Suicide 1202

Carcinomatous Syndromes 1203

ANNOTATIONS

Virilizing Action of Progestogens on the Female Foetus 1205

Antibiotics in Infantile Enteritis 1205

Infective Hepatitis and Chimpanzees 1206

Guy Fawkes Still a Threat 1206

Nursing-homes 1207

CORRESPONDENCE

Record of Antitetanus Immunization. J. P. TURNEY, F.R.C.S.; E. D. IRVINE, D.P.H. 1218

Milk Proteins in Ulcerative Colitis. B. MCNICHOLL, D.C.H. 1219

Liver Perfusion. H. J. ESPINER, F.R.C.S., and K. D. J. VOWLES, F.R.C.S. 1219

Spironolactone and Potassium Output. ARNOLD J. ROSIN, M.R.C.P., and DAVID HATCH, M.B. 1219

Steroids in Systemic Lupus Erythematosus. C. H. STEWART-HESS, M.R.C.P. 1220

SUPPLEMENT

Full Contents on First Page of Supplement

Proceedings of Council 185

General Medical Services Committee 191

Committee on Overseas Affairs 194

Correspondence:

Supply of Consultants. R. H. DAVISON, M.B.; J. MCC. MURDOCH, M.R.C.P.Ed. 198

Presentation to Mr. Waring Robinson. P. V. LANG, M.B., and others 199

G.P.'s Clinical Authority. S. W. BOWDEN, D.Obst.R.C.O.G. 199

CORRESPONDENCE—*contd.*

Safety of Canned Foods. W. HADDON, jun., M.D. 1221

Diuretics and the Eye. H. M. ROSE, M.R.C.S.; DOROTHY A. CAMPBELL, F.R.C.S. 1221

Bur for Skin Tests. JAMES MAXWELL, F.R.C.P. 1222

Carcinoma and Cushing's Syndrome. L. MOSONYI, M.D. 1222

Neuropathy after Thalidomide ("Distaval"). J. S. K. STEVENSON, M.B.; B. W. MEADE, M.D., and S. B. ROSALKI, M.R.C.P.; P. K. CAHILL, M.B. 1223

Lung Massage. S. AHMED, M.B.; R. K. SRIVASTAVA, M.B. 1224

Poliomyelitis at Hull. T. W. PRESTON, M.R.C.P. 1224

Anaesthesia for Tracheostomy in Children. D. C. CLARK, F.F.A. R.C.S. 1224

Lolly Rash? BERNARD PECK, M.R.C.S. 1224

Nuclear War. H. J. PARISH, M.D., F.R.C.P.Ed.; ELEANOR M. ETTLINGER, L.M.S.S.A.; ROBERT CUTLER, M.R.C.S.; P. H. WOODCOCK, M.B. 1225

Research and Drug Prices. M. E. LAMPARD, M.D. 1225

Oral Poliomyelitis Vaccine. W. RITCHIE RUSSELL, M.D., F.R.C.P. 1226

The Young Pretender. P. J. E. WILSON, M.B. 1226

Intravenous Iron. D. D. VORA, M.D. 1226

Presentation of Glyceryl Trinitrate. D. C. MACKENZIE, F.R.C.S.Ed. 1227

Proposed Society of Exfoliative Cytologists. M. EGERTON, M.R.C.O.G., and others 1227

Vital Statistics 1232

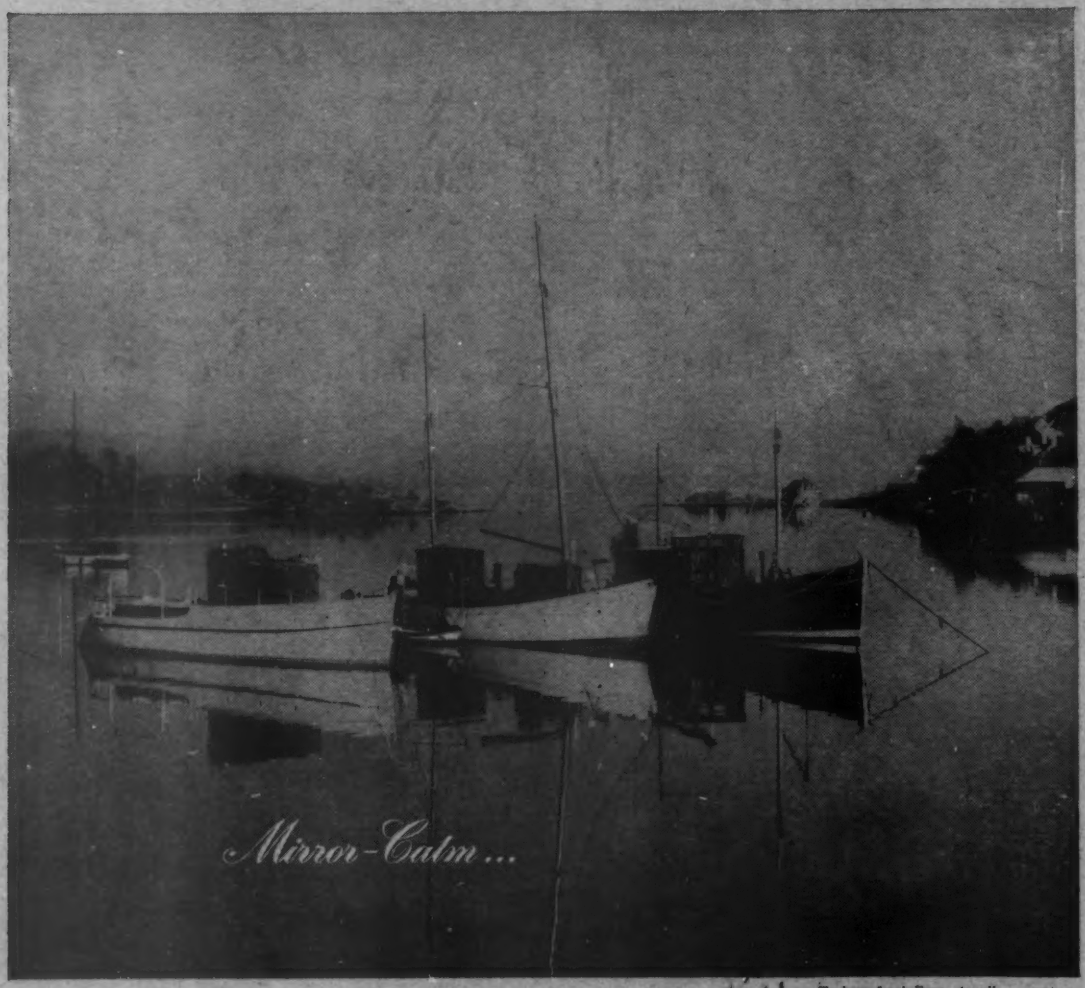
BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON W.C.1

No. 5261, WEEKLY, PRICE 3/-

Copyright © 1961

REGISTERED AS A NEWSPAPER

the tranquilliser pure and simple . . .



Tarbert, Loch Fyne, Argyll

"Thioridazine is so well tolerated that it appears an excellent phenothiazine for ambulatory patients, in particular for maintenance of patients after they leave hospital."
J. ment. Sci. (1960) **106**, 1417.

"The most striking aspect of Melleril therapy is the poverty of side-effects."
J. Amer. med. Ass. (1959) **170**, 1283.

Melleril
BY SANDOZ

Tablets: Thioridazine hydrochloride 10 mg. 25 mg. 50 mg. 100 mg.
Syrup: 25 mg. thioridazine base in 4 ml.

. . . in anxiety and agitation

BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 4 1961

PROGNOSIS OF INTRATHORACIC SARCOIDOSIS IN ENGLAND

A REVIEW OF 136 CASES AFTER FIVE YEARS' OBSERVATION

BY

J. G. SCADDING, M.D., F.R.C.P.

Director of Studies, Institute of Diseases of the Chest, Brompton

Early in 1960 I surveyed the records of 230 patients with sarcoidosis whom I had first seen up to the end of the previous year, with special reference to the role of *Mycobacterium tuberculosis* in aetiology, and in discussing them described the diagnostic criteria adopted (Scadding, 1960). A total of 136 first came under my observation before the end of June, 1955, and in the autumn of 1960 I endeavoured to complete the review of this group, first seen five years or more previously, by obtaining information about the current state of those among them who had passed out of my supervision. This paper describes the result of this review, with special reference to prognosis in relation to the intrathoracic changes.

The patients were first seen with various types of intrathoracic change, and at widely differing intervals after the probable time of onset of sarcoidosis. An earlier review of them (Scadding, 1956) had suggested that prognosis might be related to the type of intrathoracic change then found, even among those who showed no evidence of fibrosis at that time. For these reasons I have divided the patients into four groups according to the type of change in the chest radiograph when I first saw them:

Group 1: 32 patients; enlarged hilar lymph-nodes only.

Group 2: 40 patients; mottled shadowing in the lungs with enlarged hilar lymph-nodes, either present or known to have been present in the past.

Group 3: 37 patients; mottled shadowing in the lungs, without present or available past evidence of enlargement of hilar lymph-nodes.

Group 4: 27 patients; radiographic and clinical features suggesting fibrosis, usually in addition to mottled shadowing.

Groups 2 and 3 and groups 3 and 4 are not, of course, sharply demarcated from each other. It is not possible to be certain that none of the patients in group 3 had ever had enlarged hilar lymph-nodes, since such certainty would be possible only if a normal chest radiograph were available shortly before the first abnormal one; this group is therefore likely to contain, in addition to patients in whom there was in fact no stage of enlargement of hilar nodes, some in whom this stage passed without symptoms and had subsided by the time the disease was first detected. In three of them there was a record of a normal chest radiograph within three months, one year, and one year of the first abnormal one, and in 10 others there were and had been no symptoms at the time of the abnormal radiograph which was the first evidence of the disease, making it highly probable that there was in fact no stage of hilar node enlargement. The distinction between groups 3 and 4, consisting in the judgment on clinical and radiological grounds that in group 4 irreversible changes were present at the beginning of observation, cannot be regarded as precise, but in most cases decision was not difficult.

The sex distribution within these four groups is shown in Table I, together with the ages, expressed as means and ranges, when the patients first came under my observation; the estimated duration of the disease at the beginning of the observation period; and the estimated age at the time of onset of sarcoidosis, deduced from this estimated duration. In some cases the onset was marked by a definite symptom—for example, erythema nodosum or acute iridocyclitis; in others a less definite symptom was taken to indicate the onset; and in others, without symptoms, the date of the first abnormal radiograph was taken as the time of onset. As would be expected, the duration of the disease at first observation was least in group 1 (mean 6 months) and greatest in group 4 (5½ years). In groups 2 and 3 it was very similar (1¼ and 1½ years respectively); this shows that the failure to find evidence of enlargement of hilar nodes in group 3 was not due to the patients having come under observation later in the course of the disease than those in group 2.

TABLE I.—*Age-and-sex Distribution of 136 Patients with Sarcoidosis. Age at Time of Onset is Estimated from the Age When First Seen and the Estimated Duration of the Disease at that Time*

Group	No. of Patients			Age in Years when First Seen		Estimated Duration of Disease when First Seen (Years)		Age in Years at Estimated Time of Onset	
	Total	M.	F.	Mean	Range	Mean	Range	Mean	Range
1	32	15	17	28	16–47	6 12	0–2	28	16–47
2	40	11	29	30	19–51	1 6 12	6 12–11	28	18–50
3	37	17	20	34	18–54	1 9 12	1 12–5	32	18–52
4	27	13	14	41	25–55	5 6 12	6 12–20	36	22–52
Total	136	56	80	33	16–55	2 4 12	0–20	31	16–52

The condition of the patients in these four groups five years after they first came under my observation is summarized in Table II.

TABLE II.—*Condition of 136 Patients with Sarcoidosis at End of Five Years' Observation, Grouped by Condition at Beginning of Observation*

Group	Total No.	Condition after Five Years' Observation					
		Normal X-ray	Abnormal X-ray			Dead	
		No Symptoms	No Symptoms	Mild Symptoms	Severe Symptoms	Sarcoidosis	Other Cause
1	32	27	4	1	0	0	0
2	40	23	2	11	3	0	1
3	37	16	6	8	6	0	1
4	27	0	0	9	11	6	1

Group 1: Enlarged Hilar Nodes Only

The 32 patients in this group came under my observation at intervals varying from three weeks to two years after the first evidence of the disease. Twenty-three were followed for the full five years. Four were last seen after three years', one after two years', and four after one year's observation; all these were then free from all symptoms and signs of disease and with normal chest radiographs. Since no patient who attained a normal radiograph has later shown evidence of recurrent disease under further observation, the presumption that these nine patients remained well is high, and in Table II they are classed as well, with normal radiographs at five years. Including these, 27 (82%) of the 32 patients were left with no evidence of disease at five years. Two had some abnormal shadowing in the lungs, without symptoms, and three still had enlargement of hilar nodes, two without symptoms and one with slight dyspnoea on exertion and undue tiredness. During the five years' observation a total of 10 of the 32 patients developed mottling in the lung fields, at intervals varying from 1 to 10 months from the detection of the enlarged hilar nodes. Of these, eight showed complete resolution and are included among 27 without evidence of disease at five years; in the two who showed residual shadowing at five years it was interpreted at the end of this time as diminishing sarcoid infiltration in one, and as insignificant residual fibrosis in the other.

Twelve of the patients were followed longer than five years, for periods up to 10 years. Ten of these had been free from residual abnormality at five years, and two had had persistent enlargement of hilar nodes; all remained unchanged under further observation, the two with persistently enlarged hilar nodes having been last seen 6 and 10 years from the apparent time of onset.

Of 10 patients whose illness started acutely with erythema nodosum (7) or acute polyarthritis (1) or both these manifestations (2), none had residual changes, as compared with the 22 with other modes of onset, who included all five of those with residual abnormalities at five years. Two patients developed painless subcutaneous nodules near the ulnar borders of the forearms within a few weeks of erythema nodosum. These were moderately firm and elastic, about 1 cm. in diameter; one was found in one patient and several on both arms in the other. Histologically they showed the typical sarcoid structure; in both cases they subsided spontaneously within three months, and both patients were well, with normal radiographs, at five years.

Iridocyclitis was observed in 6 of the 32 patients. In five of these it was the sole extrathoracic manifestation of sarcoidosis, and in the sixth it was accompanied by transient sarcoid infiltrations of the skin over the shins. Four of the six, including the patient with skin lesions, showed complete resolution of all sarcoid lesions; the other two had radiographic abnormalities without symptoms at five years, consisting in persistent mottling in one and persistent hilar node enlargement in the other.

Group 2: Lung Shadows with Enlarged Hilar Nodes

The 40 patients in this group first came under my observation at a mean interval of one and a half years after the apparent onset of the disease. Thirty-four were followed for the full five years. Of the remaining six, one was followed for four years, four for three years, and one for two years. At this time they were all well, with normal chest radiographs, and, for the reasons given above, I have assumed, in compiling the data on which Table II is based, that they remained so throughout the rest of the five-year period. By the end of five years' observation 16 others had attained a normal chest radiograph, making 23 in all (58%) with complete radiographic resolution and freedom from other signs of sarcoidosis. Of the remaining 17, two were symptom-free but still had some faint mottling in the lungs, the hilar nodes having subsided; 11 had mild symptoms, and three had moderate to severe symptoms with radiographic abnormalities in the lungs; and one had died of an unrelated disease. In the 11 with mild symptoms the abnormality consisted in persistence of enlargement of hilar nodes only in one, and of both enlarged hilar nodes and mottled shadowing in the lungs in two, and in evidence of limited inactive residual fibrosis in eight. In the three with more severe symptoms, of which the chief was dyspnoea on exertion, there was clear evidence of fibrosis, with continued activity of sarcoidosis in two. The cause of death in the patient who died was carcinoma of the liver; at the time of death, 11 years from the onset of sarcoidosis, there was some residual shadowing in the chest radiograph, probably fibrotic, but there were no serious symptoms attributable to sarcoidosis.

Twenty patients have been followed for longer periods, up to 10 years. Of these, 16 have remained unchanged since the end of the five-year period; two have improved—one who had persistent lung mottling at five years having shown resolution by the eighth year, and one with radiographic evidence of insignificant fibrosis and mild symptoms at five years having lost her symptoms by the end of 10 years; and two have died of sarcoidosis. Of the latter two, one died of respiratory insufficiency from progressive fibrosis of the lungs 11 years after the estimated time of onset of the lung changes and 21 years after the iritis which was probably the initial symptom of sarcoidosis; and one died, 12 years after the iritis which was the first evidence of sarcoidosis, from uraemia due to hypercalcaemic nephropathy, with moderate but non-progressive fibrosis in the lungs.

Among the 23 patients whose lungs were radiographically clear after five years' observation, 18 had shown no evident extrathoracic manifestation of sarcoidosis, four had iridocyclitis, and one developed transient papular skin sarcoids on the legs after the intrathoracic manifestations had subsided. Among the 17 with persistent radiographic abnormalities, only five had no evident extrathoracic lesion, five had iridocyclitis, and no fewer than seven had sarcoidosis of the skin, of whom one had also gross hepatosplenomegaly. In group 2, as in group 1, an onset with erythema nodosum

seemed to be of good prognostic import. The illness started with erythema nodosum in seven patients, of whom six attained radiographically clear lungs.

Group 3: Lung Shadows Without Definite Evidence of Enlarged Hilar Nodes

The 37 patients in this group were first seen at a mean interval of one and three-quarter years from the apparent onset of the disease. Thirty-two were followed for the full five years. Of the remaining five, four were well, with a normal chest radiograph, when they were last seen, three after three years and one after two years, and one had limited fibrosis with no disability at three years. In Table II these five patients have been assumed to have remained unchanged for the rest of the five-year period. With these assumptions, 16 patients (43%) had attained a normal chest radiograph within five years. Six others had no symptoms, but some persistent radiographic abnormality, consisting of persistent mottling in one and slight residual inactive fibrosis in five. Fourteen had radiographic changes suggesting fibrosis, symptoms being mild in eight and severe in six. One died of mediastinal lymphosarcoma towards the end of five years' observation, nine years from the first symptoms of sarcoidosis; at the time of death there was moderate fibrosis in the lungs.

Twenty patients have been followed for longer periods, up to 13 years. Of these, 19 have remained unchanged—nine with clear radiographs, three with slight fibrosis and no symptoms, and seven with fibrosis and symptoms, mild in one and severe in six—and one has persistent mottling without symptoms or obvious fibrosis. The patient with persistent mottling has been under observation for 10 years from its first discovery. One patient with fibrosis deteriorated under further observation, and when last heard of after 13 years' observation was seriously ill with congestive heart failure.

Extrathoracic sarcoid changes were found less often in group 3 than in group 2. Of 16 patients with radiographically normal lungs at five years, two had had eye and one skin involvement; one developed heart-block, presumably from a sarcoid granuloma interrupting the bundle of His. Of the other 21, one had eye and three skin involvement, and one had gross hepatosplenomegaly. Erythema nodosum occurred in only one patient, whose lung changes resolved completely.

Group 4: Fibrosis Thought to be Present at Beginning of Observation

The 27 patients in this group first came under my observation at a mean interval of five and a half years from the probable time of onset of the disease. They are, of course, a selected group, many of whom were referred to me after prolonged periods of observation by other physicians because of an unfavourable course. It was possible to obtain evidence of an initial stage of enlargement of hilar lymph-nodes, accompanying or preceding the shadowing in the lungs, in only seven of them. In eight there was an available radiograph very early in the clinical course showing lung shadowing only, making it probable that there had been no stage of enlarged hilar nodes; and in the remaining 12 there was insufficient evidence on which to base an opinion whether there had been such a stage.

Of the 27 patients, 25 were followed for the full five years or to the time of death. The remaining two were followed for three years; at the beginning of the observation period they had had non-progressive fibrosis without evidence of activity of the sarcoidosis and with only slight disability, and their condition remained unchanged during the three years' observation. Accordingly in compiling the data on which Table II is based I have assumed that they remained unchanged for the rest of the five years. At the end of this time nine patients had mild symptoms, not preventing them from leading a normal life, 11 had more severe symptoms, though all but three were able to continue in employment or housework, and six had died of sarcoidosis and one of a cerebral haemorrhage. Of the 20 patients who survived, 10 appeared to have remained unchanged, three to have deteriorated, and seven to have shown some improvement during the five years' observation. In those who showed improvement, this could be attributed to resolution of reversible elements which had been present in the lung changes at the beginning of this period. Five of the patients who died of sarcoidosis did so in the 6th, 9th, 10th, 18th, and 25th year of the disease; in the sixth it was not possible to date the onset, since when she first consulted a physician, four years before death, established fibrosis of indeterminate duration was already present (Clinico-Pathological Conference, 1950).

Ten patients have been followed for longer periods, up to 12 years. In nine, there was no important change during this further observation, and one died from sarcoidosis in the seventh year of my observation and the fourteenth of the disease.

Extrathoracic sarcoidosis, especially of the skin, was frequent in group 4. Eight patients showed skin sarcoidosis, including three with lupus pernio and two with infiltrated scars. One other patient had multiple subcutaneous sarcoid nodules in the fingers. One had a sarcoid nodule in the breast. Two developed evidence of cardiomyopathy; since both are still alive, it has not been possible to determine with certainty whether this is due to sarcoid infiltration of the myocardium. Four have multiple bronchostenoses of the type described by Citron and Scadding (1957). No patient in group 4 had erythema nodosum at the onset of the disease or subsequently.

Corticosteroid Treatment

Observation both of the present series and of subsequent cases of sarcoidosis has led me to the firm opinion that corticosteroids have no effect upon the principal criterion of prognosis adopted in this analysis—namely, the attainment and maintenance under prolonged observation of a normal chest radiograph with freedom from symptoms. Certainly, manifestations of the disease can be suppressed while they are in a reversible stage, presumably represented pathologically by epithelioid cell granulomata without fibrosis. When in such a case the corticosteroid treatment is withdrawn, the disease may either return to its former state, seem to have been "cured" in that it does not reappear, or recrudesce to a worse state than formerly. The most reasonable interpretation of these facts seems to be that the effect of corticosteroid treatment on the disease process is purely suppressive, and that in those cases in which the disease appears to have been "cured" it would have regressed gradually even if untreated; in those in which it reappears in its former state it would have remained unchanged; while in those in which a

"rebound" to a worse state occurs after withdrawal it would have deteriorated.

When irreversible fibrotic changes in the lungs, or a very dense infiltration with sarcoid tubercles, have caused dyspnoea, unproductive cough, and other symptoms, these may be relieved to a variable degree by corticosteroid treatment. In some cases this relief constitutes a sound indication for such treatment, which may need to be continued indefinitely. There are probably two elements in the causation of such relief: the suppression of the specific cellular reaction in still active sarcoid infiltration, and favourable effects on secondary phenomena such as airway obstruction from mucosal swelling and bronchospasm. Extrapulmonary indications for corticosteroid treatment include hypercalcaemia, certainly when it produces symptoms and probably if the serum calcium remains above 12 mg. per 100 ml., and eye changes which cannot be controlled by local treatment.

This statement of my present views is necessary for two reasons as a preamble to the following description of the observed effects of corticosteroids in those patients in the present series who received such treatment. First, it explains why in the discussion of prognosis I have not thought it necessary to mention separately the minority of treated patients. And second, it provides an occasion to emphasize that the period covered by the present survey includes the time when corticosteroids were first available clinically, and that, since the experience recounted is the earlier part of that upon which the views stated above are based, many of the patients who received corticosteroids would be treated differently or not at all if they came under observation to-day.

In group 1, only three patients received cortisone for periods of three to eight weeks, soon after this hormone came into general use and before the generally favourable prognosis of patients with bilateral hilar lymph-node enlargement was fully realized. In two there was a slight reduction in size of the enlarged hilar nodes during the administration of cortisone, followed by return to the previous size on withdrawal, and spontaneous resolution within the next two years. In the third the cortisone had no effect on the enlarged nodes, which still remained enlarged, though somewhat diminished in size, after eight years' observation. It is clear, therefore, that corticosteroid treatment did not influence the outcome, and that there is no indication for such treatment in this group.

Short-term Treatment of Patients with Generalized Lung Changes

Twenty-eight patients in groups 2, 3, and 4 received cortisone for periods of three to eight weeks at the time when its effects were being explored. In three patients with established fibrosis no effect, even on the symptoms, was observed. In 25 there was partial or complete suppression of manifestations of the disease during treatment, followed by their return on its withdrawal; in 12 of these there was subsequent spontaneous resolution, and in the remaining 13 the lung changes proved persistent. Six of these 13 later had prolonged treatment with corticosteroids, and are included in the group discussed below.

Prolonged Treatment

Twenty-nine patients received prolonged treatment—20 in groups 2 and 3, and 9 in group 4. Groups 2 and 3 are considered together, since in them there was thought to be some possibility of resolution. Group 4, in which resolution was not to be expected, is considered together, since in them there was thought to be some possibility of resolution. Group 4, in which resolution was not to be expected, is considered separately.

Among the 20 patients in Groups 2 and 3, in only seven was treatment discontinued electively after substantial resolution and without subsequent recrudescence. The mean period of treatment of these seven patients was two years, with a range of nine months to four years. Two of them were left with clear lungs, and two with slight residual fibrosis but no disability; in two there was some resolution at the end of 20 months' and 32 months' treatment, and this resolution continued after the cessation of treatment, the final result being slight fibrosis with mild dyspnoea. In the seventh patient there was little change in the lungs, which showed fibrosis confined to the middle zones with little disability; prednisolone was given for the relief of pain and swelling due to involvement of the phalanges, the improvement produced being maintained when treatment was withdrawn after four years. In three patients the lung changes have progressed to irreversible fibrosis in spite of prolonged corticosteroid administration, but treatment with small doses is being continued after five, five, and six years because withdrawal gives rise to increase in dyspnoea, cough, and lassitude.

In two patients several periods of treatment during the course of two and three years respectively caused temporary suppression of radiographic shadows and relief of symptoms followed by recrudescence; after cessation of treatment, fibrosis of limited extent, apparently inactive and stable, was left, with little disability. In one no change in radiographic appearances resulted from periods of four months' and 10 months' treatment, but one year after the end of the second period of treatment partial spontaneous clearing of the shadowing was observed. In two patients there was no effect from treatment for three months in one and two periods of four months in the other; the latter developed a large gastric ulcer during the second period of treatment. In one patient skin lesions scattered over the trunk, forehead, and scalp were suppressed during three periods of treatment for seven weeks, two years, and 14 months, but recrudesced within a month or two of cessation of treatment; this patient eventually died of a mediastinal lymphosarcoma.

In the remaining four patients corticosteroid treatment was used for the control of hypercalcaemia. In one it proved possible to withdraw the hormone after 18 months, without return of the hypercalcaemia; two are continuing with small dosage of prednisolone, which remains necessary to control hypercalcaemia after more than seven years; and one, who had commencing renal insufficiency when treatment was started, required for the control of hypercalcaemia corticosteroid dosage causing important side-effects, and died in uraemia after three years' treatment. In all four patients treated for hypercalcaemia there was no more than a slight suppressive effect on the lung changes.

In summary, among these 20 patients there were only two who, after elective cessation of prolonged administration of a corticosteroid which had caused suppression of the radiographic shadows in the lungs, were left with clear lungs. It is difficult to claim that this is a better end-result than might have followed an entirely expec-

tant policy; although there can be no doubt of the partial or complete relief of symptoms, when present, and the suppression of radiographic shadowing in most cases during corticosteroid administration.

Among the nine patients with established fibrosis in group 4 who were treated, four experienced sufficient symptomatic relief to justify continued administration of small doses. One of these has been treated continuously for five and a half years; one was treated for nearly three years, deteriorated four years later, and has now been treated again for over one year with worthwhile symptomatic relief; and two—Cases 1 and 2 of Citron and Scadding (1957)—have multiple bronchostenoses and still require small doses of prednisolone to maintain symptomatic improvement after seven and six years. One other patient with multiple bronchostenoses—Case 3 of Citron and Scadding (1957)—experienced some symptomatic relief during two and a half years' treatment, relapsed to her former state when it was withdrawn, but did not wish for further treatment and remained unchanged two years later. Two patients experienced no symptomatic relief after treatment for 18 and 12 months, and the corticosteroid was withdrawn without incident. In the remaining two patients treatment was given mainly for the control of extensive skin lesions. Both of them were middle-aged women, with severe fibrosis in the lungs, and both developed hypertension with corticosteroid treatment. This gave rise to a difficult situation, since the skin lesions responded only to doses of corticosteroids which caused hypertension. One died of respiratory insufficiency after three and a half years, and the other was very severely disabled at the end of five years' observation with uncontrolled and extensive skin lesions, which on several occasions spread obviously after withdrawal of corticosteroid treatment which was given repeatedly in various forms and dosages in attempts to control them. In neither of these patients was dyspnoea from the lung fibrosis relieved in any way.

In summary, four out of nine patients with established fibrosis in the lungs experienced enough symptomatic relief to justify the continuance of long-term administration of a corticosteroid in small dosage (usually 10 to 15 mg. of prednisolone daily). Treatment of a small number of cases with skin changes indicated clearly the purely suppressive nature of the effects of corticosteroids in sarcoidosis.

These general views on the effect of corticosteroids on the evolution of sarcoidosis are in agreement with those of Sones and Israel (1960), who, in describing the course of 211 patients did not think it necessary to discuss separately the 93 among them who received corticosteroid treatment. They state that in their opinion, "although corticosteroids definitely modify the clinical symptoms and pathologic changes, the ultimate outcome of the disease is not as a rule significantly altered by the use of these agents."

Prognosis of Lung Changes in Relation to Extrathoracic Changes

Table III shows the numbers of patients in the various groups whose illness started acutely with erythema nodosum or acute arthralgia, subdivided into those who did and did not attain radiographic clearing. As in previously reported series, erythema nodosum occurred more often in women than in men, 13 women and 5 men being affected. Moreover, in three of the five men the acute illness at the beginning was characterized predominantly by a febrile arthralgia, with atypical

TABLE III.—*Incidence of Acute Onset With Erythema Nodosum or Rheumatism in Patients Whose Intrathoracic Sarcoidosis Did and Did Not Attain Radiographic Clearing, Showing the Favourable Prognostic Significance of this Type of Onset. (For All Groups Combined, $\chi^2=15.2$; $P<0.001$)*

Group	Well with Normal X-ray at 5 Years		All Others	
	Total No.	Erythema Nodosum at Onset	Total No.	Erythema Nodosum at Onset
1	27	10	5	0
2	23	6	17	1
3	16	1	21	0
4			27	0
Total	66	17	70	1

erythema nodosum. It is clear that erythema nodosum is significantly associated with enlargement of hilar lymph-nodes, having occurred in 17 out of 72 patients in whom the hilar nodes were known to have been enlarged, and in only 1 out of 64 in whom there was no evidence of such enlargement. It is also highly significantly related to the ultimate attainment of a clear chest radiograph.

On the other hand, sarcoid lesions of the skin appear to constitute an unfavourable prognostic sign (Table IV). Skin sarcoidosis was observed in 21 patients. Two of these had, in addition to sarcoid lesions of previously normal skin, infiltration of old scars, and two showed infiltration of scars only. Of the 70 who still had

TABLE IV.—*Incidence of Sarcoidosis of the Skin in Patients Whose Intrathoracic Sarcoidosis Did and Did Not Resolve Within Five Years of Observation, Showing that in the Presence of Skin Lesions the Chance of Radiographic Clearing is Less. (For All Groups Combined, $\chi^2=9.9$; $P<0.01$)*

Group	Well with Normal Radiograph at 5 Years		All Others	
	Total No.	Skin Sarcoidosis	Total No.	Skin Sarcoidosis
1	27	1	5	0
2	23	1	17	7
3	16	1	21	3
4			27	8
Total	66	3	70	18

radiographic changes at five years or died, 18 had skin lesions, as compared with only 3 out of the 66 who attained radiographic resolution. This difference is significant at the 1% level.

Table V shows the incidence of eye lesions producing clinically evident symptoms. It is clear that these are randomly scattered through all groups and between those who did and did not attain radiographic resolution, and thus have no prognostic significance in relation

TABLE V.—*Incidence of Clinically Evident Eye Lesions in Patients Whose Intrathoracic Sarcoidosis Did and Did Not Resolve Within Five Years of Observation*

Group	Well with Normal X-ray at 5 Years		All Others	
	Total No.	Eye Lesions	Total No.	Eye Lesions
1	27	4	5	2
2	23	4	17	5
3	16	2	21	1
4			27	3
Total	66	10	70	11

to lung changes. The mean incidence of 15% is much less than that reported, also from London, by Smellie

and Hoyle (1960). The difference is almost certainly to be explained by the inclusion in my series of only those cases in which the ocular changes produced symptoms and by the fact that at the time when I first saw these patients I had no special link with a department of ophthalmology.

Table VI shows the incidence of other extrapulmonary changes in the various groups. Of these, only generalized enlargement of superficial lymph-nodes (10 cases) and slight to moderate enlargement of the spleen (23 cases) were observed with sufficient frequency to

TABLE VI.—*Extrapulmonary Lesions, Other than Sarcoidosis of Skin and Eyes, Observed in 136 Patients with Intrathoracic Sarcoidosis*

	Group				Total	Chest Radiograph after 5 Years	
	1	2	3	4		Clear	Not Clear
Generalized superficial lymphadenopathy ..		5	2	3	10	4	6
Gross hepatosplenomegaly		1	1		2		2
Spleen palpable ..	4	7	8	4	23	11	12
Subcutaneous nodules	2			1	3	2	1
Infiltration of vestibule of nose ..			1		1	1	
Osteitis of bones of hands		1	1		2	1	1
Nodule in breast ..				1	1		1
Heart-block			1		1	1	
Cardiomyopathy—? sarcoid				2	2		2
Parotid swelling ..	1	1			2	2	
Swelling of lacrimal gland		1			1	1	
Facial palsy ..	1	1			2	1	1
Hypercalcaemia (causing symptoms)		2	2		4		4

justify an attempt to assess their prognostic significance. Since they occurred with about equal frequency in the 66 patients who did and the 70 who did not attain radiographic resolution, it is clear that in this series their presence did not affect the outlook in relation to the intrathoracic changes. The only other point possibly worth noting is that three serious manifestations—gross hepatosplenomegaly (2 cases), cardiomyopathy (2 cases), and hypercalcaemia causing symptoms (4 cases)—were in all instances associated with non-resolution of lung changes.

Calcification was observed to develop in lung or hilar nodes in seven certainly, and in another 11 probably, of the 136 cases (Scadding, 1961). This event tended to occur in patients with extensive intrathoracic changes, not undergoing complete resolution (even apart from the calcification). None of the seven with undoubted new development of calcification, and only two of those in whom it was probable, attained complete radiographic resolution of lung changes.

Histological evidence of involvement of the main bronchi was obtained in eight cases. In two patients in group 2 biopsy of the normal-looking mucosa in a main bronchus distorted by bronchopulmonary and hilar-node enlargement showed subepithelial infiltration with epithelioid-cell tubercles; both of these eventually were left with non-disabling residual fibrosis in the lungs and no bronchial stenosis. Six patients were first seen with bronchostenoses, four with the multiple type described by Citron and Scadding (1957) and two with narrowing of a single bronchus. All these showed atypical epithelioid-cell tubercles and fibrosis in biopsies from the narrowed bronchi. As would be expected, they were all left with permanent radiographic abnormalities and some disability.

Three patients had had frankly tuberculous manifestations—apical pulmonary tuberculosis, cervical adenitis, and pleural effusion containing tubercle bacilli—18 months to 4 years before sarcoidosis became evident. In 10 others tubercle bacilli were found during the course of sarcoidosis, on a single occasion in eight and twice in the other two, without any change in the clinical or radiological picture. The prognosis in these cases proved to be similar to that of the whole series; I have discussed this point elsewhere in relation to the larger series of 230 cases mentioned above (Scadding, 1960). Late in the course of the disease four patients underwent a change in clinical picture to that of caseating tuberculosis, with increase in tuberculin sensitivity and the appearance of tubercle bacilli in the sputum.

Ten women—three in group 1, four in group 2, and three in group 3—became pregnant during the five years' observation, two of them twice, making 12 pregnancies in all. Three of these pregnancies occurred after complete radiological resolution of the lung changes, and the lungs remained clear. Three occurred at a time when lung changes appeared to be resolving; the lungs became completely clear during the pregnancies and remained so afterwards. In two women faint abnormal mottling in the chest radiograph remained unchanged during and after pregnancy. Three women became pregnant, one of them on two occasions, when they showed widespread mottling in the chest radiograph; during these four pregnancies the shadows resolved partially or completely, only to reappear three to six months afterwards. All except one of the pregnancies resulted in a healthy child; the exception resulted in the stillbirth of twins, for which no reason was found. Thus it appears that pregnancy may cause temporary suppression of reversible elements in sarcoid lung changes, with recrudescence after delivery, but otherwise has no effect on the course of the disease.

Discussion

The associations between erythema nodosum, bilateral enlargement of hilar lymph-nodes, and a good prognosis were first described by Löfgren (1953) and have been confirmed in Europe by several other investigators (Smellie and Hoyle, 1957, 1960; Hedvall, 1960; James, 1961), and in a preliminary account of my own experience (Scadding, 1956). On the other hand, Sones and Israel (1960), in Philadelphia, where 87% of their 211 patients were negroes, found that "progressive disease and death occurred almost as often among those whose initial roentgenogram of the chest showed only hilar adenopathy as among those who had pulmonary infiltration." Moreover, erythema nodosum was rare in their series, being observed in only 6 (3%) of their patients. Thus there is in this respect an important difference between the behaviour of sarcoidosis in the North American negro and in the European.

Whether there is a difference in prognosis between patients with pulmonary infiltration who do and do not have evidence of a preceding stage of hilar-node enlargement remains uncertain. I have given reasons above for the view that in some cases there is in fact no such stage, even though it cannot be denied that in some patients who, when first observed, show only pulmonary infiltration, hilar lymph-nodes may have been enlarged in the past. Although 58% of patients who had evidence of hilar node enlargement (group 2) attained clear chest radiographs as compared with 43% of those who had

no such evidence (group 3), this difference is not significant. It is not unexpected that erythema nodosum should have been reported in the past in seven of those with, and in only one of those without, hilar node enlargement; indeed, it may well be that the latter case was one of those included in group 3 because a stage of hilar node enlargement which in fact occurred was not detected. But the incidence both of eye lesions (8% as compared with 22%) and of skin lesions (11% as compared with 20%) was notably lower in group 3 than in group 4, suggesting that patients without a stage of hilar node enlargement may represent a group in which the disease tends to remain confined, at least so far as its clinical manifestations are concerned, to the lungs.

No useful comparisons can be made between mortality rates in reported series without knowledge of the proportions of various types of cases which they include. This is likely to vary with a number of factors. In a community where routine radiography of apparently healthy populations is frequent, more individuals with symptomless intrathoracic sarcoidosis following a benign course will be discovered than in one where radiography is less widely used. Series collected from the records of diagnostic chest clinics are likely to include fewer cases with established fibrosis and more with symptomless hilar lymph-node enlargement than those derived from hospital in-patient records. Thus, Ten Have (1958) estimated mortality at only 2% among 700 cases collected from the records of chest clinics in Holland; while Nitter (1953) found that of 90 patients observed in hospitals in Oslo, 13 (14.4%) died of sarcoidosis.

My own series cannot be regarded as representative of sarcoidosis in the community as a whole, for many of the cases in group 4 were referred to me from other physicians because they were not doing well. Since the mortality observed in any series is likely to be influenced greatly by the proportions of group 1 and group 4 cases included in it, estimates of the mortality of patients found to have lung involvement in a pre-fibrotic stage are more likely to be comparable from series to series than figures for the observed mortalities of whole series. Perhaps an approximation to such an estimate can be deduced from the proportion of those patients observed with pre-fibrotic lung changes who proceeded to fibrosis, and the proportion of those first observed in a fibrotic stage who died while under observation. Adding the 10 patients in group 1 who developed radiographic shadows in the lungs to the 40 in group 2 and the 37 in group 3, we have 87 patients who were observed with pre-fibrotic lung changes; reviewing the condition of these at the end of five years' observation, I estimate that 25 would have been placed in group 4 had they first been seen at that time.

Since 6 of the 27 patients in group 4 with established fibrosis died during the five years' observation, it can be deduced as a tentative estimate that between 6% and 7% of patients with sarcoid infiltration of the lungs in a pre-fibrotic phase are likely to die as a consequence of the disease within 10 to 15 years. Among patients with disabling fibrosis, liability to death due entirely or in part to the effects of sarcoidosis must be expected to continue throughout life; as noted above, 3 more of the 136 patients included in this review have died after the end of the five years' observation. Thus the total mortality must be expected to be higher than that estimated for even a prolonged but limited period from the first detection of lung infiltration. Smellie and Hoyle (1960) give a rather similar estimate to mine of the mortality of patients with pulmonary infiltration; from Fig. 3 of their paper it may be calculated that their estimate is rather over 9%, though it is difficult to relate this figure to any specified period.

Sones and Israel (1960), using the life-table method, calculated that the survival rate for their patients 10 years after diagnosis was 84.8%, compared with a normal expectancy of 95.2%, suggesting a mortality of about 10% from sarcoidosis within 10 years. As noted above, their series included 184 negroes, among whom 50 deteriorated during the observation period and 20 died, and 27 patients of European stock among whom only 4 deteriorated and none died. The difference between the proportions deteriorating was significant at the 5% level, confirming the general impression that the disease runs a less favourable course in North American negroes than in Europeans. It is probable that the high mortality reported in several series from the United States is due to the worse prognosis among negroes. Thus, Reisner (1944), in New York, found that 7 (25%) of 28 patients, the large majority negroes, died during observation for an average period of five years; and Riley (1950), also in New York, reported 10 deaths (19%) among 52 patients, of whom 41 were negroes.

In relation to the effect of extrathoracic changes on the prognosis, similar trends were found by Sones and Israel (1960) to those shown in my series. They found that cutaneous involvement was the feature most closely associated with progressive and fatal sarcoidosis; and that this association remained significant regardless of race. They also found no correlation between prognosis and eye involvement. Smellie and Hoyle (1960) found a trend towards a worse prognosis with a greater number of extrathoracic organs involved, but this trend fell just short of significance. Although Sones and Israel found a significantly worse prognosis in patients with three or more systems involved, this difference disappeared if patients without skin involvement were analysed. The high mortality reported by Gilg (1955) in a series of 191 patients with skin sarcoidosis in Copenhagen is of interest in this connexion. Thirty-seven of them were known to have died; 20 (10.5%) were proved to have died of heart failure due to pulmonary sarcoidosis, and eight from other known causes unrelated to sarcoidosis, while in nine it was not certain whether sarcoidosis had contributed to the cause of death.

Summary

A total of 136 patients with sarcoidosis involving the hilar lymph-nodes, the lungs, or both these structures were first seen in London between 1937 and June, 1955. The condition of the lungs of these patients five years after they first came under observation is reported.

They are divided into four groups according to the intrathoracic changes at first observation.

Group 1: enlarged hilar lymph-nodes only—32 patients, first seen at an average interval of six months from the apparent beginning of the disease.

Group 2: hilar nodes and lung shadowing—40 patients first seen at average interval of 18 months from the apparent onset.

Group 3: lung shadowing without available evidence of hilar lymph-node enlargement—37 patients first seen at an average interval of 21 months from the apparent onset.

Group 4: fibrosis judged to be already present—27 patients, first seen at an average interval of five and a half years from the apparent onset.

In group 1 the good prognosis reported previously was confirmed. After five years 27 patients (84%) had clear chest radiographs and 31 (97%) were free from symptoms. Only one patient had appreciable disability.

In group 2 23 patients (53%) had attained resolution of all radiographic shadows; another 2 (5%) had some residual radiographic abnormality but no symptoms: and 11 (28%) had radiographic abnormalities with only mild symptoms. Only 3 (7.5%) had moderately severe symptoms interfering with normal life. One had died of an unrelated cause.

In group 3 16 patients (43%) had attained radiographic resolution; 6 (16%) had some residual changes with no disability; 8 (22%) had residual changes with slight disability; and 6 (16%) had moderate disability. One had died of an unrelated cause.

In group 4 six patients died of pulmonary fibrosis due to sarcoidosis in the sixth to twenty-fifth year of the disease. One died of an unrelated cause. Of the remaining 20, 10 remained unchanged, 7 showed some improvement, and 3 became worse during the five years' observation.

Only a minority of the patients were treated with corticosteroids. Reasons are given for the conclusion that this measure did not affect the principal criterion of prognosis adopted—the attainment and maintenance under prolonged observation of a normal chest radiograph.

An onset with erythema nodosum was found to be associated highly significantly with a good prognosis.

Sarcoid skin lesions were significantly associated with a poor prognosis for the lung changes.

Sarcoidosis of the eye, generalized lymphadenopathy, and palpability (as opposed to gross enlargement) of the spleen did not seem to affect the prognosis of the lung changes.

Twelve pregnancies occurred in 10 women during the observation period. During four of these pregnancies shadows in the lungs cleared, only to return after delivery. Apart from this, the pregnancies appeared to have no effect on the course of sarcoidosis.

REFERENCES

Citron, K. M., and Scadding, J. G. (1957). *Thorax*, **12**, 10.
Clinico-Pathological Conference No. 7 (1950). *Postgrad. med. J.*, **26**, 494.
Gilg, I. (1955). Kliniske undersøgerser over Boecks sarcoid. Copenhagen.
Hedvall, E. (1960). *Acta tuberc. scand.*, **39**, 249.
James, D. G. (1961). *Brit. med. J.*, **1**, 853.
Löfgren, S. (1953). *Acta med. scand.*, **145**, 424, 465.
Nitter, L. (1953). *Acta radiol., Suppl.* 105.
Reisner, D. (1944). *Amer. Rev. Tuberc.*, **49**, 455.
Riley, E. A. (1950). Ibid., **62**, 231.
Scadding, J. G. (1956). *Proc. roy. Soc. Med.*, **49**, 799.
—— (1960). *Brit. med. J.*, **2**, 1617.
—— (1961). *Tubercle (Lond.)*, **42**, 121.
Smellie, H., and Hoyle, C. (1957). *Lancet*, **2**, 66.
—— —— (1960). *Quart. J. Med.*, **29**, 539.
Sones, M., and Israel, H. L. (1960). *Amer. J. Med.*, **29**, 84.
Ten Have, H. (1958). Morbus Besnier-Boeck-Schaumann. Thesis. Gröningen.

The Royal Scottish Nursing Home in Edinburgh, which was taken over by the Nuffield Nursing Homes Trust in May last year, has now been officially reopened. It has been completely modernized and can now accommodate 48 patients. (*Scotsman*, September 29.)

THE BIRMINGHAM ORAL CONTRACEPTIVE TRIAL

BY

P. ECKSTEIN, M.D.

J. A. H. WATERHOUSE, Ph.D.
Departments of Anatomy and Medical Statistics, University of Birmingham

GLENYS M. BOND, M.R.C.S., L.R.C.P.
Medical Officer, Birmingham Family Planning Association

W. G. MILLS, F.R.C.S., F.R.C.O.G.
Consultant Obstetrician and Gynaecologist, United Birmingham Hospitals

DOROTHY M. SANDILANDS, M.B., Ch.B., B.Sc.
Medical Officer, Birmingham Family Planning Association

AND

D. MARGARET SHOTTON, M.B., M.R.C.O.G.
Consultant Obstetrician, United Birmingham Hospitals

In March, 1960, the Birmingham Family Planning Association embarked on its first oral contraceptive trial. Its objects were twofold. First, in view of the existing widespread dissatisfaction with conventional techniques of birth control, it seemed desirable to assess the efficacy and acceptability of the method among British women. Second, while the ability of relatively large doses of oral contraceptives to control fertility had been adequately established (Pincus *et al.*, 1958, 1960), there was next to no information about the effect of lower doses with regard to both the suppression of ovulation and the incidence and severity of side-effects. With these aims in mind—and that of reducing the substantial cost of the larger dosage—the Executive Council of the Birmingham F.P.A. decided to conduct a trial on a reasonably large scale and under carefully controlled conditions laid down and supervised by a specially enlisted Medical Advisory Committee.

Messrs. G. D. Searle and Co. Ltd. agreed to support the trial both financially and by supplying adequate quantities of the test material (norethynodrel) to the Medical Advisory Committee.

The following account reports findings obtained with the 2.5-mg. strength of tablet (1 OC trial). As soon as it became apparent that this dosage provided insufficient conception control, the strength of tablets taken by volunteers was increased to 5 mg. a day. Those who had not conceived up to this moment and wished to continue, as well as new volunteers not previously employed, were enlisted in further trials (2 OC and 3 OC), and to date no failures have occurred among women participating in either of these two trials in the prescribed manner. Where possible, provisional information about the results with the 5-mg. tablet is included, but a full report must be deferred until the 2 OC and 3 OC trials have been completed.

Subjects and Experimental Procedures

Selection of Participants

These were chosen from the large number of women who had responded to the appeal for volunteers. They had to satisfy the following criteria:

(*a*) *Age* under 36 years at the time of beginning the trial.

(*b*) *Proved fertility*: possession of at least one living child of the present marriage; not more abortions than children.

(*c*) *Body weight* not exceeding 11 stone (70 kg.).

(*d*) *Menstrual cycles* not varying beyond the range of 23–32 days within the past year.

(*e*) *General health* (of both volunteer and husband) must be satisfactory.

(*f*) *Coitus*: average frequency not less than once weekly.

(*g*) *Clinical examination*: normal findings at abdominal and pelvic examination.

(*h*) *Residence* within easy access of Birmingham.

All volunteers conforming to the above criteria were asked to agree to remain in the trial for a minimum of six months, and during that time to use no other form of contraceptive. It was explained to them that the efficacy of the method could not be guaranteed, and all accepted the possibility of another pregnancy in the event of failure of the tablets. In addition, each woman was required to return a consent form signed by both her husband and herself; her medical practitioner was also informed.

It had been the Committee's intention to enlist not fewer than 100 participants. Only 52 volunteers fulfilling the above criteria had been enlisted before it was decided to close the first trial. Of these 52, one was discovered to be pregnant and three others withdrew before the start of the trial, thus leaving 48 (Table I). The following report is based on the findings obtained in these 48 women.

Composition and Dosage of Test Substance

The compound selected was norethynodrel (17α-ethinyl-5(10)-oestraenolone) 2.5 mg. with 0.05 mg. of the highly potent oestrogen, ethinyloestradiol-3-methyl ether (EO-3-ME). Subsequent chemical analysis carried out in the manufacturers' laboratories in the United States revealed, however, that the oestrogen content of the batch of tablets actually used in the trial was less, and amounted to 0.036 mg.; the concentration of norethynodrel proved to be approximately correct (2.3 mg.). The tablets supplied during the 2 OC trial contained 5 mg. of norethynodrel and 0.075 mg. of EO-3-ME.

Administration of Tablets and General Procedure

Although similar in outline to other clinical trials—for example, Pincus *et al.* (1960) and Mears (1961)—there were certain differences in procedure. Counting the first day of bleeding as day 1, one tablet was taken nightly from day 5 to 24 of the cycle. Then followed an interval of eight clear days until the start of the next course of tablets, whether a period had occurred (Fig. 1*a*) or not (Fig. 1*b*). Later this interval was reduced to six days. If breakthrough bleeding occurred—here defined as bleeding before the end of a course of tablets—medication was to be stopped and a new course begun on the fifth day of the (breakthrough) bleeding (see Fig. 1*c*).

All participants were requested to maintain a regular and faithful daily record of tablet-taking, incidence of menstruation (including "spotting"), sexual intercourse, and side-effects on specially provided diary cards (Fig. 2). These were given to them together with bottles containing 20 tablets—enough for one full course—of norethynodrel, and had to be returned after the completion of either one or two courses to the F.P.A. clinic before new supplies were issued.

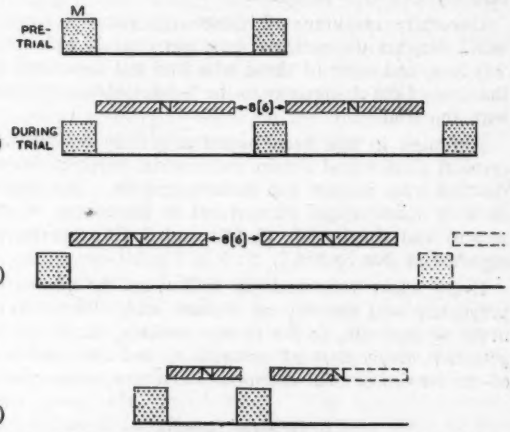


FIG. 1.—Diagrammatic representation of experimental procedure. M, menstruation; N, course of norethynodrel. (*a*) Normal sequence of cycles (above, pre-trial; below, during trial). (*b*) Amenorrhoea. (*c*) Breakthrough bleeding.

The women were also advised to disregard minor ailments (such as a cold), but in the event of more serious illness to consult either the medical officer in charge of the trial or their own practitioners.

All volunteers were interviewed and, if necessary, examined when reporting at the end of every second course of medication. In the event of amenorrhoea (exceeding, initially, six weeks), they were asked to collect specimens of urine and dispatch them to the clinic for (Aschheim–Zondek) pregnancy tests. If the test was negative but amenorrhoea persisted, repeat tests were carried out at intervals of a few weeks until the diagnosis was established.

The first volunteers started on the medication—and with it the trial as a whole began—in June, 1960. When, approximately three months later, it became evident that several conceptions had occurred, all women were asked to report to the clinic without delay, where the position was explained to them. They were

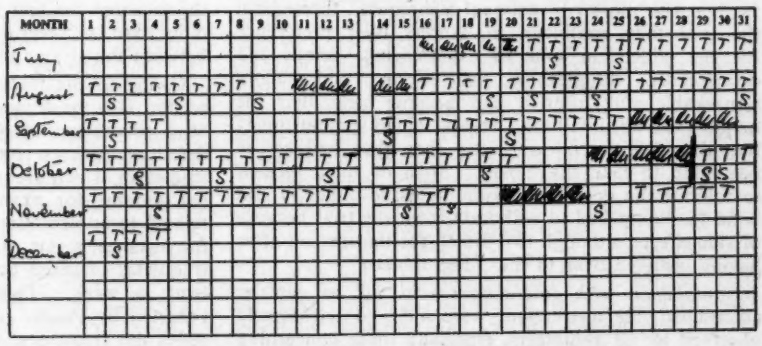


FIG. 2.—Photocopy of volunteer's diary card during trial. T, tablets; ▮, bleeding; S, sexual intercourse; ▮, transfer to 2 OC trial (October 29, 1960).

then asked to complete the current cycle and to start a new course (on the fifth day of bleeding, as usual) with a fresh supply of 5-mg. tablets issued to them. If menstruation was delayed, they were to use conventional methods of contraception before beginning to take the new type of tablet.

Generally speaking, all these arrangements worked well. Neither the patients' trust nor contact with them was lost, and most of those who had not conceived by the time of the changeover to the 5-mg. tablets continued with the trial.

Although it had been hoped originally to examine cervical smears and obtain endometrial biopsies during the first trial, neither was in fact possible. The results of such examinations carried out in the course of the second and third trials (2 OC and 3 OC) are to be reported in due course.

Every effort was made to follow up the course of pregnancy and delivery of women who conceived, in order to ascertain, so far as was possible, the length of gestation, likely date of conception, and the condition of the newborn. All deliveries have now taken place.

I. General Results

A total of 48 women embarked on the trial, of whom 14 conceived (see section II below, and Table I).

TABLE I.—*Distribution of Cases*

Originally enrolled	52
Removed before start of trial	4*
Included in first trial (1 OC)	48
Conceived	14
Did not conceive while on trial	34

* Voluntary withdrawal, 3; pregnant before trial, 1.

The remaining 34 subjects have been transferred to the second trial (2 OC; 5-mg. tablets), and while continuing on it none of them had conceived up to the time of writing—a period extending in some cases to almost a year.

The observations on menstrual periodicity and side-effects assembled below (sections III and IV) are based mainly on the records of the women who did not conceive and were therefore transferred to the second trial; in those that became pregnant the first few cycles before the established occurrence of conception have also been included in the analysis.

Acceptability of Method and Compliance with Instructions

Acceptability.—Taking the group as a whole, the method proved highly acceptable. Many of the women had joined the trial because of their professed dissatisfaction with more conventional techniques; throughout the trial they continued to express their preference for the tablets, in spite of experiencing various and occasionally disagreeable side-effects, and, more remarkable still, after it had become clear that the method was not infallible. Several stated spontaneously that they felt "well" or better than they had before beginning to take the tablets. Most of them seemed to tolerate the compound without undue difficulty and none felt compelled to withdraw from the trial because of side-effects, although two did so for that reason after having changed over to the 5-mg. tablets.

Compliance with Instructions.—So far as can be ascertained, the instructions were most conscientiously observed by all volunteers, especially those concerning the daily taking of tablets, recording this and the other required details on the diary cards, and applying for fresh supplies of norethynodrel when necessary. All cards were regularly and rigorously scrutinized, both when returned to the clinic and repeatedly during the survey on which this report is based. Except in cases of breakthrough bleeding, there were no more than six occasions on which tablets were missed. In all but one of them the deficiency amounted to only a single tablet, and was compensated by taking two tablets the next day in accordance with instructions. Such minor deviations have been ignored. The one exception was the omission of three consecutive tablets in one cycle, but this was followed by a normal menstrual period. Apart from these few isolated cases we are satisfied that the tablets were taken in the manner and numbers prescribed, and that failure by the volunteers to do so was not responsible for the observed low efficacy of the compound.

Group Comparisons

All the more important details about the participants of the survey are listed in Table II. It shows that they were divided into two main sections, according to the interval between successive courses of medication. This was first set at eight days, but in the case of later entrants to the trial it was set at six days (cf. Fig. 1). Once allotted to a given division, each woman remained in it throughout the trial, and the second one (2 OC) as well.

TABLE II.—*Group Comparisons*

	All Subjects	Non-pregnant		Pregnant	
		8-day	6-day	8-day	6-day
No. of cases	48	12	22	6	8
Mean age (years)	29·0	30·4	28·0	30·2	28·8
Mean weight (pre-trial)	9 st. 3·8 lb.	9 st. 1·2 lb.	9 st. 4·6 lb.	9 st. 7 lb.	9 st. 3 lb.
Previous children	2·5	2·6	2·1	3·3	2·5
Previous miscarriages	0·4	0·3	0·3	1·0	0·5
Average duration of course* (days)	27·9	28·5	29·3	25·5	25·7
Average No. of tablets per course	19·1	19·2	19·2	18·5	19·2
Average No. of courses per woman	2·69	3·67	2·09	3·00	2·63
Frequency of intercourse†	22·4%	20·4%	22·5%	21·3%‡	27·5%

* Defined as not fewer than 12 consecutive tablets. † For basis of calculation see text. ‡ Based on five women only (see text).

Since pregnancies occurred in both divisions, each volunteer fell into one of four groups. Table II lists for comparison the principal characteristics of these four groups and of the series as a whole. Apart from the fact that the first women to be enlisted were a little older than later recruits, no major differences are shown between the groups in any relevant respect.

Owing to the marked variation in cycle length (see section III), the frequency of coitus has been expressed as a percentage of the total days in the trial. This definition permits comparison with the results of other studies in which frequency of intercourse is expressed per month—for example, Pincus *et al.* (1960)—or is related to an arbitrary cycle of 28 days. On this basis, for instance, a rate of 25% would represent an average frequency of seven times per month, or approximately twice a week. This figure agrees well with those reported by Pincus *et al.* (1960). In one case of our series the frequency of coitus was unusually high: as it would have unduly affected the mean of the group concerned, the smallest of all, it has been excluded (see

footnote to Table II); it was also excluded from the mean frequency for the series as a whole.

Because of the occurrence of breakthrough bleeding (see section III), the courses of medication showed considerable variation in length. In 80% of all courses, 16 or more tablets were taken, and in 10% 10 or fewer. For convenience the figure of 12 or more tablets has been taken as constituting a *course*. The average duration of a course has been obtained by relating the days in the trial to the number of tablet-courses of 12 or more. These are the conventions used in Table II. It shows that there were no important differences in the length of courses so defined between the various groups of subjects; in the smallest one, however, it averaged 18.5 tablets compared with 19.2 in the rest.

II. Pregnancies

The most important, if unlooked-for, result of the trial was the occurrence of pregnancy in nearly one-third of the participants. Eleven of these resulted in 12 healthy liveborn infants, including one pair of twins. Of the three remaining pregnancies, two ended in miscarriage, while in the third this diagnosis is highly probable but could not be established with absolute certainty (Table III). In at least four and possibly six instances fertilization appears to have taken place during the first course of medication.

TABLE III.—*Conception Related to Tablet Failure*

Tablet Failure*	No.	Pregnant and Delivered	Miscarried
Definite	11	9	2
Probable	2	1	1†
Doubtful	1	1	—
Total ..	14	11	3

* See section II.
† Diagnosis of miscarriage not established with absolute certainty.

We have classified the conceptions into three grades: *definite*, where we are satisfied that pregnancy was undoubtedly due to tablet failure; *probable*, where there was some slight element of doubt, but the balance of evidence was markedly towards a tablet failure; and *doubtful*, where the evidence, though suggestive of failure, was equivocal. Each case has been reviewed in the light of all the information available, which includes details from the patient of tablet-taking, bleeding, and dates of intercourse; dates and results of pregnancy tests; period of gestation and probable time of conception, calculated from birth date; birth weight; and signs of prematurity or postmaturity.

Of the 14 conceptions, 11 were graded as *definite* tablet failure, two as *probable*, and one as *doubtful* (see Table III). If this last case is omitted from the survey the number of conceptions believed to be due to failure of the compound becomes 13 out of 48, or 27%. In a further woman subjected to hysterectomy (for prolapse) after four courses of tablets, a large ripe corpus luteum was observed in one ovary at operation, thereby increasing the proportion of cases showing no inhibition of ovulation to 14 or almost 29%. It may be added that in the single case of twins born during this series the babies were of the fraternal binovular type.

The pregnancy rate has also been related to days in the trial, and thence to a basis of 100 woman-years. It is thus exactly comparable to other published rates given in this form (see, for example, Tietze, 1960). Excluding the one doubtful case, the rate is 130 conceptions for 100 woman-years. Expressed in terms of the average course of tablets (27.9 days; see Table II), it is equivalent to a conception rate of 10%.

Condition of the Newborn

In view of the unusual, and possibly unique, character of the series, special efforts were made to follow up the 11 cases of pregnancy until parturition and in particular to record the state of the babies at birth. Most of the deliveries were domiciliary ones, and the following summary is based on the observations made by the doctors concerned in reply to a specific questionary.

There were 10 single births and one pair of fraternal twins. All were liveborn after apparently normal pregnancies and have survived; only one, a female, was premature, weighing 5 lb. 6 oz. (2,440 g.) and being born after a gestation of 36 weeks.

Of the 12 babies born, 6 were males (including the twins) and 6 females—approximately the expected sex ratio. In none of the females were there any signs of malformation or virilization of the external genitalia or other noticeable abnormalities. The more important data collected about the pregnancies and state of the babies at birth are shown in Table IV.

TABLE IV.—*Details of Deliveries and Babies*

Serial No.	Sex	Weight lb. oz.	Weight g.	Gestation (Weeks)	Delivery	Genitalia	Remarks
3	F	7 14	3,570	42	Spontaneous	N.A.D.	"A little postmature"
4	F	5 6	2,440	36	,,	,,	Previous history of 5 premature babies
8		Miscarriage		10	—	—	
15	F	6 11	3,035	38½		N.A.D.	Slight jaundice
17	F	7 13	3,545	42	Surgical induction		No evidence of postmaturity
19	F	6 12	3,060	38	Spontaneous	,,	
22	M	6 3	2,805	40	,,	,,	Assisted breech delivery
23		Miscarriage*		10	—	—	
24	M	8 8	3,855	40½		N.A.D.	
25	M	9 0	4,081	41½	Spontaneous	,,	
33	F	7 4	3,290	41	,,	,,	
34	M	7 0	3,175	40	,,	,,	
37	{M	6 5	2,865}	39½	,,	,,	
	{M	7 4	3,290}				
46		Miscarriage		9	—	—	

* Diagnosis not fully established.

Neither delivery nor lactation appears to have been affected by medication during pregnancy. This was, of course, restricted to a period of, at most, two months around the time of conception and involved only very small doses of norethynodrel. Even so, the apparent complete lack of adverse effects on either mothers or babies concerned should be stressed especially because of the various reports of such effects following exposure to oral contraceptives that have appeared in recent years (Wilkins *et al.*, 1958; Grumbach *et al.*, 1959; Wilkins, 1960).

III. Menstrual Cycle

Cycle Length

Table V shows the distribution of cycle length. This has been obtained according to the conventional definition, counting from the first day of bleeding up to and including the day before the start of the next period. "Spotting" was recorded by 18 of the 48 women (37.5%) in the series. It occurred on a single

occasion in 15 of them and twice in the rest. It has been ignored in the computation of cycle length. None of our volunteers had got beyond four cycles before the trial was closed.

TABLE V.—*Distribution of Cycle Length*

Days	Cycle				Before Entering Trial	
	1st	2nd	3rd	4th	Stated	Actual*
<20	(14)	(17; 17; 19)	(14)			(19)
20	1	1		1		
21		1	1			
22	2			1		
23	1		2	1		2
24	3	2			1	3
25	1	2			2	5
26	5	2	2		11	7
27	2	1		1	6	9
28		3	2		20	4
29	1	4			1	6
30	2		2		6	1
31	2	1	1		1	4
32	5			1		1
33	2	1				1
34	1		1	1		1
35	1					
>35	(37; 40; 42; 44; 44; 44; 47; 49; 49; 52; 55; 60; 67)	(36; 37; 38; 40; 45; 46; 51)	(39; 42; 55)	(38)		(40; 43)
Total	43	28	15	7	48	47
Mean	33·9	29·6	30·0	28·0	27·5	27·9
Median	32	28	28	27	28	27
>35 days	31%	25%	20%	14%	0	4%

* Duration of cycle immediately preceding entry into trial. (For one patient this figure was not recorded.)
The figures in parentheses are the actual cycle durations when either <20 or >35.

The most noticeable effect has been a lengthening of the cycle. More than a quarter of all cycles observed during medication were of more than 35 days' duration, and over half of our volunteers had at least one cycle exceeding 35 days. As can be seen, the proportion of these prolonged cycles consistently diminished with time. The incidence of short cycles (<20 days) was relatively low (5.3%) (see Table V).

As a better measure of average in a distribution which is clearly very skew, the median has been given in addition to the mean. It represents the middle in rank, as many being below as above that figure. Both median and mean show a progressive diminution with time consistent with the reduction in the number of prolonged cycles.

Participants in the trial were asked at the original medical examination to state their normal menstrual pattern and the date of their last period. They entered the trial on the fifth day of their next menstrual period, details of which were to be recorded on their diary cards. From this information the last two columns of Table V have been compiled, showing the distribution of "stated" and "actual" cycles. A very much wider variation is apparent in the actual compared with the stated, and there is also some evidence for preferences of certain numbers (26, 28, 30) in the latter group.

Duration of Period

Table VI, laid out in a similar form to Table V, shows the distribution of the length of the period after each of the cycles on the tablet, as well as the stated and actual pre-trial lengths. Oddly, the last two columns show the reverse effect to that shown in Table V, for the variation is greater in the stated group than in the actual. The periods following the first and second (tablet) cycles both show increased variability, which diminishes in the succeeding two periods. Although this pattern fits in with the experience of other observers, the reduction in variability in our series may be a consequence of the small number of women who experienced as many as four cycles.

TABLE VI.—*Duration of Period*

Days	Cycle				Before Entering Trial	
	1st	2nd	3rd	4th	Stated	Actual*
2	2	3	1		1	
3		1	2	1	8	1
4	12	5	1	1	3	11
5	17	13	10	4	21	25
6	7	3	1	1	8	9
7	3	2			6	
8	2					1
9		1			1	
Total ..	43	28	15	7	48	47
Mean ..	5·02	4·82	4·53	4·71	5·04	4·98
Median	5	5	5	5	5	5

* Duration of period immediately preceding entry into trial. (For one patient this figure was not recorded.)

Breakthrough Bleeding

Nearly one-third of the tablet courses were cut short by breakthrough bleeding (defined as any interruption before the completion of a course of 20 tablets). Breakthrough was least frequent in the first course of medication, and when it occurred was relatively late—on average on the 21st day of the cycle, at which time there remained only three more tablets to be taken. In subsequent courses the interruption was earlier and was probably the result of ovulation delayed from the preceding cycle (see also Discussion).

When transferring to the second trial after the close of the first, each volunteer had to await the onset of a menstrual period before starting on the double-strength tablets. During the changeover the intermenstrual interval was often prolonged, as observed in other trials (see Searle and Co., 1961a).

IV. Side-effects

In the trial as a whole, side-effects were relatively infrequent and slight. Observations on their occurrence and on changes in weight during the trial are based on 34 subjects who were eventually transferred to the 2 OC trial and five others who contributed experience during one or two cycles before conceiving (cf. section I).

Of this total, 27 subjects (69%) experienced so few, infrequent, and trivial symptoms as to remain virtually free of them (classified as "none or very slight"). In a further seven (18%) side-effects were present but were moderate in character and usually confined to the first or second course of medication, improving or disappearing afterwards ("slight or moderate").

Only five women (12%) recorded more persistent or severe and usually multiple symptoms ("marked"), but, even so, found them tolerable and none withdrew from the trial on their account; two, however, did so after the changeover to 5-mg. tablets.

Because of their highly variable distribution it has been impossible to express individual symptoms on a percentage basis or relate them to the sequence of courses of medication experienced by the group as a whole. Much the most common complaints were headache, often but not invariably accompanied by nausea and sickness and swollen, tender breasts. Between them these accounted, in roughly equal proportions, for some 62% of all symptoms recorded by the subjects. Another important group was backache and abdominal or pelvic pain, at times described as cramp, but distinct from uterine pain ("dysmenorrhoea"). This, too, was

common (about 19%) but generally slight, although in one instance it was intense enough to cause the subject concerned to faint. The only other effects recorded were vaginal discharge (not previously present) and dizziness, either alone or associated with nausea and vomiting. With the progress of the trial there was a tendency for symptoms to become less severe or to disappear.

Changes in Weight.—In addition, volunteers frequently experienced some changes in weight. In one-half of the subjects this amounted to minor fluctuations not exceeding 3 lb. (1,360 g.). In 12 (32%) there was a rise averaging 5 lb. (2.270 g.), and in 7 (18%) a similar fall. In some instances the gain, though considerable, was temporary, and was later followed by a corresponding loss and return towards the pre-trial weight. There appeared to be no consistent or marked correlation between changes in weight and other side-effects of the type referred to above.

Effect of Changeover to 2 OC Trial.—As a rule, transfer to the 5-mg. dosage caused pre-existing symptoms to be intensified or, in subjects previously unaffected, to appear for the first time. In two instances this was sufficient to induce withdrawal from the trial. In most of the remainder, however, the condition improved gradually, and few subjects who continued on trial 2 OC as prescribed for more than a few months appear to have experienced troublesome side-effects. Many of them, in fact, have spontaneously recorded their well-being and improvement in general condition as the result of the medication. Changes in weight, even if considerable earlier on, also tended to become less as the second trial proceeded.

Discussion

Fertility Control

The reported findings leave no doubt that the tablets used in this trial did not provide adequate protection against conception. The proportion of pregnancies that occurred—14 out of 48 or approximately 29%—is much higher than that observed with conventional methods of birth control. If the survey is restricted to "undoubted tablet failures" (see above) the figures are almost unchanged (27%). Expressed differently, they imply a ratio of about 130 conceptions per 100 woman- (or exposure-) years (Pearl, 1939; Stix and Notestein, 1940; cf. Tietze, 1960). This compares with an overall pregnancy rate of 2.7 per 100 exposure-years during medication with 10-mg. tablets of norethynodrel in some 500 Puerto Rican volunteers (Pincus *et al.*, 1960), and is as high as that in completely unprotected subjects. Thus the pregnancy rate in white women not practising contraception is of the order of 80 (60–100) per 100 exposure-years (Tietze, 1960); it was about 200 in a group of Puerto Rican women either before or after withdrawal from the trial (Pincus *et al.*, 1960; Searle and Co., 1961a).

Taken at their face value these findings seem to conflict sharply with the increasing body of opinion indicating that a 2.5-mg. strength of norethynodrel provides conception control sufficient in itself and comparable to that of the 5-mg. and 10-mg. tablets (Pincus, 1960a; Pincus *et al.*, 1960; Medical Advisory Council Family Planning Association, 1960; Napp, 1960; Searle and Co., 1961a; Mears, 1961).

It may be that we were dealing with a group of women of quite exceptional fertility. They were, however, drawn from basically the same population as that which normally attends the Birmingham Family Planning Clinic and previously achieved a similar measure of protection with standard methods such as diaphragms and jellies. The further fact that none of the women who were successfully transferred from the first to the second trial and continued on it have conceived also suggests that they were not exceptionally fertile. The possibility that only the women affected, rather than the rest of the group, failed to take the tablets satisfactorily has already been considered and discounted (see section I).

A much more likely explanation of the ineffectiveness of the tablets is their low content of oestrogen. This, as stated, was 0.036 mg. of EO-3-ME per 2.5-mg. tablet, or approximately 1.4%.

A relatively low oestrogen/progestin ratio had been agreed on in consultation with the manufacturers supplying the tablet, in a deliberate attempt to reduce the incidence of side-effects, such as nausea and other gastro-intestinal symptoms, which are commonly ascribed to the oestrogenic moiety of the compound. This proved to be unjustified. Although the incidence and severity of side-effects in our trial were somewhat lower than reported elsewhere (Pincus *et al.*, 1960; Tyler, 1960; Searle and Co., 1961c), they were accompanied by considerable derangement of the menstrual cycle (such as prolonged amenorrhoea; see section III) and further offset by the almost complete failure to prevent ovulation.

It is well established that oestrogens by themselves can reduce the amount of gonadotrophin released by the anterior pituitary and thereby interfere with ovulation (Dodds, 1961). Their exact role as ovulation inhibitors in oestrogen-progestin mixtures like norethynodrel ("enavid") is not clear, but it is generally agreed that they contribute to, even if they are not wholly responsible for, the antiovulatory effect (Tyler, 1961).

Effective conception control coupled with relative stability of the endometrium appears, however, to require a minimal complement of oestrogen of the order of about 0.075 mg. and preferably 0.1 mg., irrespective of the total progestin content; the amount of EO-3-ME in the tablets used at Birmingham was 0.036 mg. and was presumably below the critical value. Perhaps the most important result of the present study—in spite of its unexpected and disappointing clinical aspects—is that it provides new information clearly supporting such a conclusion. This appears to be consistent with the views of other workers, such as Tyler (1961) and Mears (1961); it is also shared by the manufacturers themselves (Searle and Co., 1961b). It would be of considerable theoretical interest to study the ability of pure or more nearly pure preparations of norethynodrel to suppress ovulation and control menstrual cyclicity.

In certain circumstances even as low an amount of oestrogen as that in the Birmingham trial may provide adequate fertility control. This was reported by Pincus (1960b) in a small group of Puerto Rican women taking 2.5-mg. tablets of norethynodrel containing only 0.0375 mg. (1.5%) and 0.05 mg. (2%) of EO-3-ME. All of them had, however, previously used, and had been controlled by, higher dosages of 5 and 10 mg., with correspondingly greater oestrogen contents.

Again, the above considerations do not necessarily apply to other racial groups, in particular subjects of much lower average body weight, such as Japanese and

Indian women. Information on this aspect is almost completely lacking, but would be well worth while collecting.

It must therefore be concluded that the oestrogen content of the compound used in the present trial was too low—either in absolute amount or in relative proportion to norethynodrel—and thus responsible for the inadequate contraceptive efficacy of the tablets.

Effects on the Cycle

It had been anticipated that the low dosage of norethynodrel employed would result in a high incidence of premature or breakthrough bleeding. This was, in fact, not observed, and a significant feature of the trial was the prolongation of cycles induced by the compound.

Compared with an average of 27.9 days (median 27 days) during the last pre-trial cycle, the mean length during the first cycle under medication was 33.9 days (median 32), and of the total of 43 cycles recorded 13 (31%) lasted for more than 35 days, with maxima of 60 and 67 days (see Table V). Although the number, both absolute and relative, of such prolonged periods progressively diminished with time, the tendency towards a lengthening of the cycle during the trial cannot be questioned.

The reasons for the occurrence of this phenomenon, which was first observed during the trials with 10-mg. tablets, are not clear (cf. Pincus *et al.*, 1960). In the case of very low doses of norethynodrel, as used in the present trial, the most likely explanation is that the compound did not suppress but merely delayed ovulation from one to the subsequent cycle, to be followed either by premature bleeding or, in the event of coitus, by conception. This suggestion cannot be substantiated, since no tests to establish the occurrence of ovulation were carried out; but it is supported, in the cases of pregnancy, by retrospective analysis of birth dates and relating them to the recorded data of sexual intercourse. It is also the explanation advanced in the account by Mears (1961).

On the other hand, the incidence of short cycles, or what is commonly referred to as breakthrough bleeding, was unexpectedly low, cycles of less than 20 days' duration totalling only five. Since isolated episodes of slight bleeding or "spotting" were not considered when computing cycle length, this figure may not be comparable with those reported in other trials and which appear to range from 20 to 30% for women using either 5 or 2.5 mg. of norethynodrel (Tyler, 1960; Napp, 1960; see Searle and Co., 1961c).

Side-effects

Side-effects were generally slight and tolerable, and in this respect the original aim of the trial was realized.

The average number of cycles experienced by individual subjects was, however, small and the findings, though suggestive, do not permit any ultimate conclusions. It was also noticeable that in a large proportion of volunteers the changeover from the 2.5-mg. to 5-mg. tablet tended to accentuate existing symptoms or to bring them on in women who had been free of them on the lower dosage. This tendency was most pronounced soon after the changeover—when two volunteers felt unable to continue and withdrew—but diminished with the progress of the second trial. A similar initial intensification of side-effects appears to have been observed in other surveys in which the reverse change, from a higher to a lower dose—for example, 10 mg. to 5 mg.—of norethynodrel was made (Tyler, 1960; cf. Searle and Co., 1961c).

Summary

A trial has been carried out to test the acceptability and contraceptive efficacy of norethynodrel in a carefully selected and supervised group of women of proved fertility.

With the view to reducing side-effects as well as cost, a low dose of norethynodrel was chosen. The tablets actually used in the trial contained 2.3 mg. with 0.036 mg. of oestrogen (ethinyloestradiol-3-methyl ether).

The tablets were generally acceptable, but, although taken in strict conformity with instructions, failed to control fertility.

Of 48 subjects enrolled, 14 (29%) conceived, resulting in 11 pregnancies and three miscarriages. Ten single babies and one pair of twins have been born; all were healthy and there were no signs of virilization of females or other noticeable abnormalities among them.

The remaining 34 volunteers who had not conceived before the trial was closed were changed over to tablets containing 5 mg. of norethynodrel and 0.075 mg. of oestrogen. No pregnancies have occurred in the women who continued to take this dosage as instructed.

During the trial side-effects such as headache, nausea, tender breasts, and abdominal pain were relatively frequent but were usually slight and tended to diminish with time; the same was true of changes in weight. No participants withdrew because of these effects.

The tablets, however, caused derangement of the cycle, as a rule towards prolongation, short cycles (or breakthrough bleeding) being unexpectedly rare.

The results obtained are compared with those of similar trials reported in the literature.

It is suggested that with doses of norethynodrel as low as 2.5 mg. the concentration of oestrogen becomes critical and, if below it, may reduce or abolish the contraceptive activity of the compound, probably by delaying ovulation rather than completely inhibiting it.

We wish to pay tribute to the former chairman, now president, of the Birmingham Family Planning Association, Mrs. Lella Florence, whose interest and enthusiasm were responsible for the inception of the trial; and, equally, to her successor, Mrs. A. K. Court, and her colleagues, Mrs. M. A. MacMillan and Mrs. E. V. Hill, on the staff of the clinic, without whose steady and capable support it could not have been conducted. We also acknowledge our indebtedness to Messrs. G. D. Searle and Co. Ltd., High Wycombe, Bucks, and their medical director, Dr. G. R. Venning, both for the supply of the tablets of norethynodrel and for substantial financial help and advice during the progress of the trial. Finally we wish to thank all those anonymous volunteers who by agreeing to participate in the trial and by their conscientious record-keeping made the whole investigation possible.

References

Dodds, E. C. (1961). *J. Endocr.*, **23**, No. 3, p. i.

Grumbach, M. M., Ducharme, J. R., and Moloshok, R. E. (1959). *J. clin. Endocr.*, **19**, 1369.

Mears, E. (1961). *Brit. med. J.*, **2**, 1179.

Medical Advisory Council, Family Planning Association (1960). *Brit. med. J.*, **2**, 380; *Lancet*, **2**, 256.

Napp, E. (1960). Quoted in Searle and Co. (1961c).

Pearl, R. (1939). *The Natural History of Population*. Oxford Univ. Press, New York. Quoted by Tietze (1960).

Pincus, G. (1960a). *Acta endocr. (Kbh.)*, **34**, Suppl. 50, p. 135.
—— (1960b). Quoted in Searle and Co. (1961c).
—— Rock, J., and Garcia, C. R. (1960). *Proceedings of the Sixth International Conference on Planned Parenthood, New Delhi, 1959*, p. 216. International Planned Parenthood Federation, London.
—— —— —— Rice-Wray, E., Paniagua, M., and Rodriguez, I. (1958). *Amer. J. Obstet. Gynec.*, **75**, 1333.
Searle, G. D., and Co. (1961a). Conovid for Fertility Control. *Reference Manual*, No. 85.
—— (1961b). *Investigators Manual*, March, 1961.
—— (1961c). Symposium: Clinical Experience with and Practical Techniques for the Use of Enavid in Ovulation Control, New York, January, 1961. In *Data on Norethynodrel*.
Stix, R. J. K., and Notestein, F. W. (1940). *Controlled Fertility*. Williams and Wilkins, Baltimore. Quoted by Tietze (1960).
Tietze, C. (1960). *Proceedings of the Sixth International Conference on Planned Parenthood, New Delhi, 1959*, p. 275. International Planned Parenthood Federation, London.
Tyler, E. T. (1960). The Use of Norethynodrel in Fertility Control. Paper read to the Endocrine Society, June, 1960.
—— (1961). In Symposium: Clinical Experience with and Practical Techniques for the Use of Enavid in Ovulation Control. (See Searle and Co., 1961c.)
Wilkins, L. (1960). *Acta endocr. (Kbh.)*, **35**, Suppl. 51, p. 671.
—— Jones, H. W., jun., Holman, G. H., and Stempfel, R. S., jun. (1958). *J. clin. Endocr.*, **18**, 559.

CLINICAL TRIALS OF ORAL CONTRACEPTIVES*

BY

ELEANOR MEARS, M.B., Ch.B.

Medical Secretary, Council for the Investigation of Fertility Control, London

It has been known for some years that the steroids existing in nature could inhibit ovulation in woman. Practically, however, these steroids were not of value as anti-fertility agents, because of either the undesirable side-effects produced or the lack of therapeutic effectiveness on continued therapy. For example, testosterone produces undesirable androgenic effects; progesterone requires very large doses and its action is too variable; and oestrogens, although they will inhibit ovulation in some cycles, are claimed by some workers not to do so in every cycle (Drill, 1959); while long-term administration of oestrogen is complicated by irregular menstrual bleeding, which may be heavy.

Pincus and his colleagues in 1955 first found that some newer orally active steroids, mostly 19-nor compounds, would inhibit ovulation in the rat and the rabbit. This finding initiated extensive endocrinological and clinical testing of these compounds. Over 200 new steroids have been tested, but the two which have been most used are norethisterone and norethynodrel. Norethynodrel, which has been subjected to most intensive study by Pincus and his colleagues, appeared to be particularly interesting, as it was the first steroid to possess both progestational and oestrogenic activity in the same molecule.

These early trials showed that 10 mg. of norethynodrel ("enavid") plus 0.15 mg. of ethinyloestradiol-3-methyl ether (EO-3-ME) taken for 20 days from day 5 of the cycle was an effective contraceptive, and there was no indication of escape from contraceptive effect with time. Side-effects which occurred in a significant proportion of subjects—particularly vomiting, nausea, dizziness, headache—were found to be more frequent in the first cycle of medication and to decrease thereafter. The addition of oestrogen to the progestogen itself was found to be necessary to maintain the endometrium and prevent spotting and breakthrough bleeding, though this still occurred despite regular taking of tablets. On the whole, patients had regular bleeding and a decreased menstrual flow. Of Pincus's volunteers, 20% gave up in the first year, largely because of these side-effects, while among Tyler's more sophisticated women in Los Angeles 474 out of 715 (66%) discontinued.

As the side-effects and high cost were a disadvantage, 5-mg. tablets containing 0.075 mg. of EO-3-ME were tried and found to be equally effective, and later 2.5 mg. had been used with varying amounts of oestrogen and with apparently similar results.

These early trials were watched in this and other countries with interest and caution: would there be any harmful effects from pituitary inhibition, any possible carcinogenic effect from the administration of steroids; would fertility be restored when the tablets were discontinued? By 1959 it seemed that these anxieties were unjustified, and preliminary carefully controlled clinical trials were instituted under the auspices of the Council for the Investigation of Fertility Control (chiefly undertaken by Dr G. I. M. Swyer and Dr. Margaret Jackson) of some of the available oral progesterones. In 1960 the Medical Advisory Council gave careful consideration to the question of the advisability of using the progestational steroid norethynodrel plus oestrogen as a contraceptive under the conditions planned for clinical trials and was satisfied that it would be safe to use in the way planned. At that time the total experience of norethynodrel included over 20,000 cycles of administration in over 1,000 women, including 150 who had received norethynodrel from 12 to 21 consecutive cycles and 66 women who had taken it from 24 to 38 consecutive cycles.

Large-scale clinical trials were then initiated, the first in Birmingham, followed soon after by another in Slough, and a third has recently begun at the Family Planning Association Headquarters in London.

Thus it will be seen that the trials initiated by the Council are of two distinct kinds: first, small, carefully controlled preliminary trials of a more scientific nature, and later large-scale clinical trials.

Preliminary Trials

Before any of these substances are used in clinical trials on women, careful consideration is, of course, given to the data available from the manufacturers, including particularly the animal screening tests for acute and chronic toxicity, and for androgenic, progestogenic, and oestrogenic properties. When it is felt that enough is known at this level, the substances are used in a number of tests which have been devised for preliminary screening in women.

These tests are usually undertaken with the pure progestogen and with the progestogen with added oestrogen.

1. *An assessment of the ability to postpone menstruation in women with regular cycles.*—An appropriate dose such as 5 mg. is administered daily from the twentieth day of the cycle for 20 days. If menstruation occurs before the 20 tablets have been taken, the result is negative and the test is repeated in the following cycle with double the dose. If menstruation does not occur until after completing the course, the result is positive and the test is repeated with

*Paper read at the Annual Conference of the Society for the Study of Fertility, at Cambridge, June, 1961.

half the dose. This test gives a measure of progestational activity by which comparison with other products of known potency can be made, though it does not necessarily parallel inhibition of ovulation, etc. It also gives some indication of tolerance and acceptability and necessary dosage

2. *To assess the ability to inhibit ovulation.*—It is believed that basal temperature charts and endometrial biopsies may be confirmatory but not convincing. Measurement of pregnanediol excretion is necessary in humans. The products to be tested are given daily from the fifth day of the cycle for 20 days. Urine is collected on the eighth and ninth days and on the twentieth and twenty-first days, in 48-hour pools, and the pregnanediol excretion determined. Where inhibition of ovulation occurs there is no difference in pregnanediol excretion between the two samples.

3. *To investigate the ability to produce secretory changes in the endometrium.*—In this test, women with long-standing secondary amenorrhoea are used and are treated as follows: ethinyloestradiol 0.05 mg. daily is given for 20 days and the progestogen in whatever dose has seemed most satisfactory from previous tests is given daily from the eleventh to the twentieth day. After an eight-day gap without medication, this routine is repeated regardless of the appearance of bleeding. Endometrial biopsy is taken the day after the last pill in this second cycle of administration.

It will be seen that these preliminary tests give us some indication of the tolerance in humans and of the capacity to inhibit ovulation, and also a measure of progestational activity on the endometrium. Such data have already been collected on norethynodrel, norethisterone, norethisterone acetate, B.D.H. 1298 (6α-methyl,$\triangle$-6-17α-acetoxyprogesterone) with and without added oestrogen and in various doses, and tests are proceeding with other substances.

It is apparent so far that these compounds are all much more effective when used with added oestrogen, which rather suggests that the pituitary inhibition is also responsible for cutting down the production of endogenous oestrogen, thus necessitating exogenous administration of the latter. Although these products have similar effects on inhibition of ovulation, cervical mucus, and the endometrium, there are some interesting differences.

When a progestogen is found as a result of such preliminary tests to be suitable for use as an oral contraceptive, it is then used in a small number of women as a contraceptive. If the results are satisfactory over a few months, the product is ready for use in large-scale trials.

Large-scale Clinical Trials

Once the background data have been obtained, it is obvious that larger-scale clinical trials are necessary, the object of such trials being to establish (1) the strength of pill that will produce minimal side-effects with adequate control of conception; (2) the simplest method of administration; and (3) the acceptability of the method to women in this country.

The organization of large-scale trials is described in the preceding report (p. 1172) of the Birmingham trial (Eckstein *et al.*, 1961) and need not be repeated here.

Method of Administration.—The routine we are using differs from that of other workers, as it was decided that there was no point in repeating the same experiments. The pills are given in bottles of 20—that is, each bottle contains one month's supply. The patients are instructed to take one pill daily from the fifth day of the cycle for 20 days (the first day of the cycle is the first day of menstruation); they then stop taking pills, wait until withdrawal bleeding occurs—usually one to four days later—and start the new bottle on the fifth day of the next menstrual cycle. They are told that if no menstrual bleeding occurs they should leave five clear days and again start a new bottle of pills.

In trials elsewhere (Pincus, 1959, 1960; Pincus *et al.*, 1958, 1959; Rock, Garcia, and Pincus, 1959), the question of breakthrough bleeding has been dealt with by getting the patient to increase the dose, taking one extra tablet each day when breakthrough bleeding threatened, and to continue this until spotting disappears. It seemed to us possible that the menstrual cycle might settle down after three or four cycles and the breakthrough bleeding stop spontaneously. The regime we decided to use, therefore, was that if slight staining or spotting occurred the patient should ignore it and continue to take the tablets; if bleeding occurred which was as much in amount as normal menstruation, she should discontinue the tablets, allow the bleeding to take place, and resume them again on the fifth day of the cycle as before. It seemed to us simpler to give the patients a regular number of pills to take each month. As norethynodrel has been used most extensively it was the one chosen in the first large-scale clinical trials in this country.

Dosage Used.—As workers in other countries were already using 2.5 mg., and since it seemed to be as effective as larger doses, could be expected to give fewer side-effects, though rather more breakthrough bleeding, and had already been used with varying amounts of oestrogen, it was decided to concentrate on this dose, and to try out 2.5-mg. tablets of norethynodrel with varying amounts of oestrogen. The earliest clinical trials were undertaken by Dr. Swyer, Dr. Margaret Jackson, Dr. Helena Wright, and myself, using 2.5 mg. of norethynodrel plus 0.15 mg. of EO-3-ME. In the first trial in an F.P.A. Clinic (Birmingham 1 OC) the dose used was 2.5 mg. of norethynodrel plus 0.035 mg. of EO-3-ME, and in Slough F.P.A. Clinic a few weeks later a third strength, 2.5 mg. plus 0.1 mg. of EO-3-ME.

Birmingham 1 OC Trial

As a detailed account of this trial is given earlier in this issue (see p. 1172), all that need be said here is that it soon became obvious from the record charts of patients in the Birmingham trial that this tablet was having a different effect from the others.

The first noticeable difference with patients in the Birmingham trial was that their menstrual cycles were irregular: 20 cycles lasted 30 days or more, up to as many as 71 days; 7 were less than 25 days, with very few around the normal limits. It quickly became obvious that in fact some of the patients were pregnant, and that this tablet was not an effective contraceptive, as it seemed to *delay* ovulation rather than to inhibit it.

It would appear that when patients came to the end of 20 days' issue of tablets they had a breakthrough ovulation and consequent amenorrhoea with, in several cases, breakthrough bleeding in the middle of the next cycle. Since the 2.5 mg. with 0.1 and 0.15 mg. of oestrogen was proving efficient, it was shown that at the 2.5-mg. dose the amount of oestrogen is critical. This raises the whole question of whether 2.5 mg. of norethynodrel is a sufficiently high dose to inhibit ovulation and whether in fact tablets with a larger proportion of oestrogen have worked because of the oestrogen and not the norethynodrel. Investigations carried out in Puerto Rico by Tyler (1961) and Napp (1960) indicate that this is a sufficient dose there to inhibit ovulation. (This raises

some interesting questions of the dose required for women in different parts of the world.)

This result means, too, that we cannot use a quarter of an enavid 10-mg. tablet or half of a "conovid" 5-mg. tablet, as in the smaller dose a larger proportion of oestrogen is required.

When this failure became evident, patients in the Birmingham trial were switched over at the end of their current cycle to 5-mg. tablets of conovid—that is, tablets containing 5 mg. norethynodrel plus 0.075 mg. of EO-3-ME. In the first place the volunteers who were switched over from this tablet to the 5-mg. tablet have been analysed separately (Trial 2 OC). Later volunteers who were put straight on to the 5-mg. tablet comprise those in Trial 3 OC.

As can be seen from Table I, there is no significant difference between those who started on the 5-mg. pill and those who started on the smaller dose and were transferred to the 5-mg. pill, except that the amount of nausea in the first cycle is less among patients transferred to the higher dose. This is to be expected, as these patients had already developed some tolerance to the drug.

TABLE I

No. of Women	No. of Woman-months	Nausea	Nausea and Vomiting	Dysmenorrhoea	Headache and Faintness	Weight Increase > 3 lb. (1·36 kg.)	Weight Decrease < 3 lb. (1·36 kg.)	Breakthrough Bleeding
F.P.A. Birmingham Trial (3 OC) 5 mg. Norethynodrel + 0·075 mg. EO-3-ME								
(*a*) 35	35	43%	9%	11%	17%	17%	11%	31%
(*b*) 22	22	14%	14%	23%	9%	23%	9%	36%
(*c*) 19	19	Nil	Nil	11%	5%	16%	5%	37%
(*d*) —	31	6%	Nil	16%	6%	13%	32%	32%
Birmingham 2 OC Patients Transferred from Lower Dose to 5 mg. Norethynodrel + 0·075 mg. EO-3-ME								
(*a*) 34	34	29%	9%	9%	15%	35%	3%	18%
(*b*) 31	31	13%	6%	19%	9%	13%	6%	35%
(*c*) 30	30	7%	3%	7%	3%	7%	3%	23%
(*d*) —	70	10%	3%	3%	7%	17%	4%	24%
(*e*) —	11	9%	9%	9%	18%	18%	Nil	15%

(*a*) = 1st month. (*b*) = 2nd month. (*c*) = 3rd month. (*d*) = months 4, 5, 6. (*e*) = other months.

TABLE II.—*Analysis of Results on Different Doses of Norethynodrel and EO-3-ME*

Months	No. of Women	No. of Woman-months	Nausea	Breast Discomfort	Show	Breakthrough Bleeding
5 mg. Norethynodrel + 0.075 mg. EO-3-ME						
1	91	91	48%	30%	30%	27%
2	66	66	20%	24%	28%	25%
3	61	61	Nil	16%	20%	26%
4, 5, 6	—	184	4%	27%	15%	24%
Others	—	15	Nil	10%	12%	15%
Total	91	350				
2·5 mg. Norethynodrel + 0·1 mg. EO-3-ME						
1	35	35	54%	26%	20%	34%
2	30	30	13%	7%	3%	33%
3	26	26	4%	8%	4%	38%
4, 5, 6	—	63	Nil	9%	8%	30%
Others	—	27	7%	4%	11%	63%
Total	35	181				
2·5 mg. Norethynodrel + 0·15 mg. EO-3-ME						
1	89	89	42%	Not available for all patients	9%	27%
2	75	75	24%		7%	34%
3	73	73	10%		4%	22%
4, 5, 6	—	166	4%		4%	23%
Others	—	186	Nil		2%	22%
Total	89	589				

It is possible, therefore, to add these together for a comparative analysis of the different doses. Table II is such an analysis, excluding, of course, the Birmingham 1 OC trial with the ineffective dose.

Side-effects

There seems little to choose between the different doses of tablets. The incidence of *nausea* in every case is highest in the first month at about 40% and rapidly diminishes thereafter.

There appears to be no significant *change in weight*—some patients gain, a few lose weight, but no relationship has been found between change in weight and premenstrual tension, breakthrough bleeding, or show.

Libido.—The effect on libido reported in other trials has been variable. Rock and Garcia found that in 50% of patients the libido was unchanged, in 25% it increased, and in 25% it decreased. In our trials patients are asked to record the number of times of sexual intercourse and are asked at interview whether libido has been affected. More patients claim to have increased libido; a few to have a decrease. This seems to me, however, to be a factor which is not easy to analyse in such a statistical way—for example, we have no record of the number of times of intercourse before the trial began, and experience of my own patients leads me to doubt the significance of such figures. Thus one patient, who had not marked any intercourse on her chart for two months, said on questioning that when she had a diaphragm and put it in she felt that it was a pity not to use it and she roused her husband. Since she had been protected all the time by the pill and since she preferred her husband to take the initiative, she had waited for him to do so with this result. Another patient claimed that her libido had decreased since using the tablet, but on looking up her previous records I found that a year beforehand, when she had come for refitting of her diaphragm, she had made the same complaint. On being reminded of this she indicated that there had been no decrease since that time. At the other end of the scale is the couple who marked up intercourse 91 times in one month—whether this can really be ascribed to the pill is doubtful. It must surely have had something to do with the husband's libido.

Efficiency

In the Birmingham 1 OC trial—that is, with 2.5 mg. plus 0.035 mg. EO-3-ME—there were 14 pregnancies out of 48 women. In seven women conception probably occurred in the first cycle and in three in the second cycle. This has given some most valuable information. We know now that at this dosage the amount of oestrogen is critical and the lowest dose which will inhibit ovulation is now reasonably well known to us.

There have been no pregnancies in the Birmingham 2 OC trial—that is, in those who switched from this tablet to the 5-mg. tablet—or in the Birmingham 3 OC trial—that is, in patients joining the trial on the 5-mg. dosage. In the Slough trial with 35 patients continuing for 181 woman-months on 2.5 mg. of norethynodrel plus 0.1 mg. of FO-3-ME, there has been one pregnancy, in a patient who had taken her tablets only intermittently. There is no question of tablet failure with this patient who took only 7 out of 20 tablets in the month she became pregnant.

So far, 89 women have taken tablets containing 2.5 mg. of norethynodrel plus 0.15 mg. of EO-3-ME for 589

woman-months. There has been one pregnancy, a tablet failure, among these women. This is a patient aged 36 with two children aged 13 and 6, who had a perineal tear repaired four times, with a great deal of anxiety over pregnancy, and who claims to have had no sexual relationships for several months before starting the pill. She was extremely relaxed and confident when she first started using the pill, had amenorrhoea in the first cycle, left five clear days and started the second bottle of pills as directed. She felt extremely well in the first month but began to have nausea which did not wear off. Her weight increased and she began to be anxious shortly after starting the second course of tablets. On February 12 she was found to have a positive Hogben test and pelvic examination on February 14 confirmed the diagnosis.

The tablets were obviously taken conscientiously; the patient insists that there was no question of pregnancy before she started taking them, and I am certainly inclined to believe her. Could this be a case where the tablet failed to inhibit ovulation in the first cycle or only delayed it, or is the dose too little for this patient, or could it be that the excitement associated with renewal of intercourse after such a gap could overcome the effect of the pituitary inhibition produced by the norethynodrel? After all, this happens sometimes when a woman ovulates a second time in the cycle under such circumstances.

It is interesting to notice that Pincus found among women who conceived in his trial that most conceptions occurred in the first month, and he says, "The data suggest a greater carelessness in the early cycles of experience." On the other hand, Tyler (1959) recommended the use of a diaphragm and jelly in the first month in some cases. Is it possible that some patients are not fully covered in the first month of medication? It will be some time before we know the answer to this.

Acceptability

Much prominence has been given everywhere to the side-effects complained of by patients in the early months of using oral contraceptives, but something should be said about the positive effects mentioned by patients.

Many patients have expressed themselves as being absolutely delighted with the freedom from contraceptive measures related to coital acts, of being more confident and relaxed at intercourse, and other interesting observations have been made—for example, discharge gone, skin improved, hair less greasy, abdominal post-operative pain gone, feeling better than ever before, first orgasm ever, cut down smoking, dysmenorrhoea gone. The real indication of acceptability to the patient, however, is presumably whether she perseveres with this method, and so far the results are encouraging.

Table III is an analysis of patients who have withdrawn from the trial. It will be seen that only 25 patients are included in the group taking the 2.5 mg. plus 0.15 mg. tablets: this is because full particulars are available only for patients in one of the trials at this dosage. Considering the proportion of patients who do have some side-effects in the beginning, this number of withdrawals due to side-effects from the tablets seems remarkably small. It will be seen that nine patients out of a total of 150 withdrew for this reason.

TABLE III.—*Withdrawals*

Tablet Strength	No. of Patients	No. of Woman-months	Total No. Withdrawing	No. Withdrawing Because of Side-effects of Pill
5 mg.+0·075 mg.	91	350	7	2
2·5 ,, +0·1 ,,	35	181	5	3
2·5 ,, +0·15 ,,	25	272	6	4

5 mg.+0.075 mg. (conovid)

1. 1st month—no reason given.
2. 1st month—dizziness and blurred vision.
3. 5th month—wishing to become pregnant.
4. 3rd month—heavy feeling, amenorrhoea.
5. 6th month—aches and pains all down left side of body.
6. Husband gone away } Both may rejoin.
7. Marital difficulties }

No. due to tablet side-effects: 2 (months 1 and 3)

2.5 mg.+0.1 mg.

1. 3rd month—nausea.
2. 6th month—increase in weight.
3. 6th month—short cycles.
4. 1st month—discharge.
5. 3rd month—pregnant, due to intermittent tablet-taking only.

No. due to side-effects: 3 (months 3, 6, 6).

2.5 mg.+0.15 mg

1. Pregnant 1st month.
2. 6th month—abdominal cramp, constant lethargy, and feeling cold.
3. 14 cycles, all with breakthrough bleeding, sick headaches, abdominal cramp, and growing antipathy to taking pills for rest of life.
4. Gave up at 6th cycle because of mastitis, breakthrough bleeding in five out of six cycles, increased weight, bloated feeling.
5. Gave up after eight months because of migrainous headaches every month and depression in the period without tablets and sleeplessness, though very reluctant to stop as she liked this method of contraception very much.
6. 4 cycles: an erratic user, forgot one month, took 24 another month, frigid, dislikes birth-control methods, etc.; when I queried her over being erratic she took fright and left.

No. due to side-effects: 4 (months 6, 6, 8, 14).

Breakthrough Bleeding

To test the value of our regime, the breakthrough bleeding has to be analysed. For the purpose of our trials, breakthrough bleeding is defined as bleeding of an amount equal to that of a normal period, so that the patient stops medication.

It would appear from the figures so far that there is very little to choose between the different strengths of tablets in the first six months, as can be seen from the comparative figures for each month in Table IV. The small number of patients on the 5 mg. and the 2.5 mg. plus 0.1 mg. tablet who have continued beyond six months makes the figures for breakthrough bleeding beyond that time of little value so far. The patients, however, who have continued the 2.5 mg. plus 0.15 mg. tablet have continued for some time. Among my own 25 patients on this dose one patient has continued for 20 cycles and several for more than 12 cycles, and here the percentage of persistent breakthrough bleeding is 22%, so that, on this tablet, one can say that on this regime about 20% of patients can expect to continue to have breakthrough bleeding beyond the sixth month. There is no reason to suppose that this breakthrough bleeding is harmful in any way; endometrial biopsies repeated on patients who have continued to have such short cycles show hypoplasia of the endometrium and, in fact, suggest that a higher proportion of oestrogen in the tablet might be more effective in preventing this phenomenon.

The average *length of breakthrough bleeding cycles* on the different tablet strengths was analysed to find out if there was any difference. It has been suggested, for example, by Napp (1960), that the breakthrough bleeding tends to occur in the earlier part of the cycle on the smaller dose. This has not been our experience.

For this analysis, cycles where tablets were missed were discounted and all cycles are included where the tablets were taken conscientiously.

TABLE IV.—*Analysis of Breakthrough Bleeding Cycles*

Tablet Strength	No. of Cycles of B.T.B.	No. of Days	Average Length of B.T.B. Cycle
2·5 mg. + 0·1 mg. ..	33	700	21
2·5 ,, + 0·15 ,, ..	27	591	22
5 ,, + 0·075 ,, ..	23	465	20

TABLE V.—*Patients Transferred to 5 mg. from Lower Strength Because of Persistent Breakthrough Bleeding*

No. of Cycles of B.T.B.	No. of Days	Average Length
34	677	20

In some of the patients, where breakthrough bleeding has been persistent, an attempt has been made to control this by increasing the dosage to 5 mg. but administered in the same way. In no cases so far has this reduced the breakthrough bleeding (Table V).

On the other hand, there seems no reason to worry about breakthrough bleeding of this order where the cycles are 20 to 22 days in length, and some patients have been perfectly happy to carry on in that way.

Nevertheless, some attempts have been made to control this. Among my own patients, two who have been transferred to Schering 639 (4 mg. of norethisterone acetate + 0.05 mg. of ethinyloestradiol) have immediately settled down to a normal cycle, and two patients who have been given an increased dose in the second half of the cycle have also settled down.

The amount of menstrual flow is interesting, and I have made an analysis of my own patients (25 on 5 mg. and 25 on 2.5 mg. + 0.15 mg.) who mention any increase or decrease in the amount of flow: 22% found a decreased flow and 8% found an increased flow. In all these cases, however, those who had had heavy bleedings before treatment had less heavy bleeding during treatment, and those who claim to have earlier and prolonged bleedings had all very slight ones in the first place.

Amenorrhoea

Sometimes withdrawal bleeding fails to occur with a consequent cycle of amenorrhoea. The number of cycles of amenorrhoea in these trials has been analysed (Table VI).

TABLE VI.—*Amenorrhoea*

Tablet Strength	Cycles of Amenorrhoea	Woman-months	Percentage
2·5 mg. + 0·1 mg. ..	17	181	9
2·5 ,, + 0·15 ,, ..	3	272	1
5 mg. + 0·075 mg. ..	21	344	6

Pincus (1959) suggests that after withdrawal of medication the endogenous ovarian secretion takes over and is adequate to sustain the endometrium. The incidence of amenorrhoea reported by Pincus (1959) in trials in Humacao, Puerto Rico, and Haiti has been between 0.7% and 3.2%, so that our regime would appear to increase its incidence.

Conclusions

Much has been learnt about the mechanics of running trials of oral contraceptives.

We have discovered that with a 2.5-mg. dose of norethynodrel the amount of oestrogen is critical; 0.035 mg. of ethinyloestradiol 3-methyl ether is not sufficient combination, with the progestogen, to prevent ovulation. There is therefore not enough oestrogen in half a conovid tablet for effective use.

Bearing in mind that these patients have all proved their fertility, this would appear to be a most efficient method of contraception in the right dosage. So far 215 women have taken part in the trials for 1,120 woman-months and only one pregnancy has occurred where the tablets have been taken conscientiously.

There seems to be little to choose so far between the different doses of norethynodrel used. About 40% of the patients have some degree of nausea in the first month, but this very quickly disappears if they are encouraged to persevere. The only other important side-effect after the first month is breakthrough bleeding. The regime we have initiated in trials in this country does not appear to solve this problem. About 20% of patients can expect to continue to have breakthrough bleeding beyond the fourth cycle. While this is not considered to be harmful, it can be annoying to the patient, and it would seem advisable to have more than one product available, as such patients may settle well on another product.

It would appear that the American method of increasing the dosage when breakthrough bleeding threatens might be a better method of controlling this, but we feel that it is a clumsy method and one which could be improved upon.

I am grateful to all the doctors who have carried out this work and for permission to include their figures: Dr. Bond in Birmingham, Dr. Newbury and Dr. Pullen in Slough, Dr. Swyer, Dr. Margaret Jackson, and Dr. Helena Wright.

The members of the Clinical Trials Committee of the Council for the Investigation of Fertility Control are Dr. G. I. M. Swyer (chairman), Dr. P. M. F. Bishop, Dr. Margaret Jackson, Professor R. J. Kellar, Professor G. F. Marrian, Professor A. S. Parkes, Miss D. M. Shotton, and Dr. Eleanor Mears (medical secretary).

REFERENCES

Drill, V. A. (1959). *Fed. Proc.*, **18**, 1040.
Eckstein, P., Waterhouse, J. A. H., Bond, G. M., Mills, W. G., Sandilands, D. M., and Shotton, D. M. (1961). *Brit. med. J.*, **2**, 1172.
Medical Advisory Council of the Family Planning Association (1960). Ibid., **2**, 380; *Lancet*, **2**, 256.
Napp, E. (1960). Personal communication to G. D. Searle and Co.
Pincus, G. (1959). *Proceedings of the Sixth International Conference on Planned Parenthood, New Delhi, 1959*, p. 234. International Planned Parenthood Association, London.
—— (1960). Fertility Control by Endocrine Agents. *First International Congress of Endocrinology, Copenhagen, 1960.*
—— Rock, J., and Garcia, C. R. (1959). *Proceedings of the Sixth International Conference on Planned Parenthood, New Delhi, 1959*, p. 216. International Planned Parenthood Association, London.
—— —— —— Rice-Wray, E., Panigua, M., and Rodriguez, I. (1958). *Amer. J. Obstet. Gynec.*, **75**, 1333.
Rock, J., Garcia, C. R., and Pincus, G. (1959). *Proceedings of the Sixth International Conference on Planned Parenthood, New Delhi, 1959*. p. 212. International Planned Parenthood Association, London.
Tyler, E. T. (1959). Ibid., p. 231.
—— (1961). Symposium: Clinical Experience with and Practical Techniques for the Use of Enavid in Ovulation Control. New York, January, 1961.

A new school curriculum introduced by the Minister of Education in Greece has abolished Latin, cut down the time spent on studying ancient Greek, instituted systematic teaching of modern Greek, and increased the time spent on teaching mathematics and physics.

INJURIES FROM FIREWORKS

BY

DOUGLAS JACKSON, M.D., F.R.C.S.

Burns Unit, Birmingham Accident Hospital

Historical

In 1604, the year after James I came to the throne, a plot was hatched to destroy the King and his Government by blowing up the Houses of Parliament. Guy Fawkes, who was the tool of more influential people, was chosen for the dangerous task of setting fire to the gunpowder when Parliament opened on November 5, 1605. But the plot miscarried. Fawkes was arrested as he went to take up his position in the cellars the night before, and the other conspirators were killed or taken prisoner.

Great was the rejoicing at this deliverance. Bonfires were lit and bells rung: and even now, after more than 350 years, the day is still remembered in Britain with bonfires and fireworks.

Few anniversaries can be accompanied by such a trail of injury and suffering throughout the length and breadth of the country. Each year, as this day comes round, explosives are put into the hands of children, who have had little or no instruction or training, so that they may enjoy themselves. The results are what one would expect.

This is no modern development. From the early seventeenth century firework displays were given to mark national celebrations. Commercial pyrotechny, too, was well established. Pepys (1633–1703) describes obtaining "an abundance of serpents and rockets" which his friends flung about, "burning one another and the people over the way" (Brock, 1950).

Richard Wiseman (1705), surgeon to Charles II, also makes detailed reference to a firework injury he treated:

"A young gentleman of about ten years of age, boarded at a School a few miles off, the Evening before the fifth of November having filled his right Pocket full of Squibs and Crackers, threw one of them into the Chymney amongst the Embers. It took fire: but whether it scattered the Fire, and some parts of that flew into his Pocket, or whether it was the Cracker, but those in his Pocket took fire also, and his Cloaths burnt. At the sight whereof his little Chamberfellow ran out for help. In his absence a little Boy from some other Apartment took the alarm, came in, and seeing his School-fellow in a flame, catch up a Bason of water, and threw it upon him; then ran away for help. Others came in and rescued him out of his burnt Cloaths. A neighbouring Chirurgeon was sent for, who dressed him. The next day they brought the Patient to Town. I found him burnt into the Flesh from a hand's breadth below that Arm pit down that Side, with part of his Belly, and from thence it spread down to the Os ileon and Gluteus, and along the Thigh almost to the knee. And by endeavouring to free his Pockets of the Cracker, he also burnt his Hand from the fingers ends along the side of his Arm to his Elbow-joynt."

After describing his treatment in detail, he concludes:

"Thus I happily cicatrized this young Gentleman's Ulcers even and smooth without the least Inequality, nothing remaining but the red colour to make it discernable."

The Position To-day

For the past 13 years a record of firework injuries on November 5 has been kept at the Birmingham Burns Unit (Table I). Each year casualties number 30–50; two-thirds are males, and three-quarters are under 15 years. A total of 510 casualties occurred from November 5 celebrations in 13 years. Shocking though this figure appears, it is a gross underestimate of the problem, for firework injuries begin two weeks before the 5th and continue for several days after. For example, on November 5, 1951, rain stopped play: there were 4 casualties on the 3rd, 3 on the 4th, and 21 on the 6th, making a total of 55 over four days. Again, in 1955 there were 15 further casualties on November 6. In Birmingham the ambulance drivers are directed to bring

TABLE I.—*Guy Fawkes Injuries* (*November 5 Only*), 1948–1960

Year	No. of Casualties	Firework Held in Hand	Face and Eyes	Fireworks in Pocket	Loaded in Clothing or Wellington Boot	Thrown or Kicked	Jumping Firework	Mis-aimed Firework	Opened Firework Gunpowder Lit	Bonfire
1948	31	—	—	—	—	—	—	—	—	—
1949	34	25	5	0 (0)	1 (0)	2	0	1	0	0
1950	60	29	11	4 (4)	0 (0)	0	0	0	0	0
1951	27	18	3	0 (0)	2 (0)	5	0	0	0	0
1952	52	26	2	2 (1)	3 (0)	6	2	3	1	3
1953	40	15	6	4 (3)	4 (0)	0	0	2	0	1
1954	31	15	8	2 (2)	2 (1)	1	2	1	0	1
1955	52	32	6	3 (1)	2 (0)	3	0	2	4	3
1956	37	16	3	6 (5)	0 (0)	3	1	0	0	2
1957	25	5	5	6 (4)	1 (1)	1	2	4	0	4
1958	31	7	2	5 (4)	2 (0)	1	3	3	0	1
1959	38	9	9	9 (6)	4 (1)	3	0	1	0	3
1960	52	9	10	7 (5)	4 (1)	7	1	2	2	7
Total	510	206	70	48 (35)	25 (4)	32	11	19	7	25

Figures in parentheses indicate number operated on.

firework and bonfire injuries to the burns unit, except for eye injuries occurring in isolation, which are taken to the Midland Eye Hospital. It is probable, therefore, that the unit receives about 90% of the firework injuries requiring hospital attention from Birmingham and the surrounding few miles—a population of about 2 million people.

A study of the causes of injury has shown the following trends.

Fireworks Held in the Hand

The commonest cause of injury until 1956 was undoubtedly fireworks held in the hand. Almost half of the injuries were blast effects, occasionally resulting in loss of a finger or phalanx, but more usually splitting the pulp and raising haematomata. The other half were burns, or mixed burn and blast injuries. In 1950, a bad year for this type of case, two patients lost a finger, and one lost part of the index: the youngest victim was a baby of 15 months who received a deep laceration of the hand; he cried and asked to hold a "banger," so his parents let him.

Even when "bangers" are clearly labelled "Not to be held in the hand" it is not surprising that this is overlooked in the environment where these accidents occur—perhaps a dark street with a crowd of boys larking about. Some boys give a history of picking up a "dud" which has failed to go off, and which then explodes in the hand: 15 of the 32 cases in 1955 gave this story—a feature perhaps associated with the very wet day.

In 1957 we were astonished to receive no blast injuries of the hands, and this change has persisted. The reason is clear. Prior to 1957, for some 30 to 40 years, the common "banger" on sale in the United Kingdom was

a penny or twopenny "thunderflash" with a bursting charge of aluminium (or magnesium) and a chlorate. This was a very potent mixture. After the war the sale of fireworks increased greatly, and particularly the thunderflash: this was partly because fireworks had been banned altogether during the war and a generation had grown up which knew nothing of them. In the later months of 1956 the trade agreed voluntarily to discontinue the manufacture of thunderflash fireworks in an effort to reduce noise and to forestall criticism from the public on this ground. They further agreed with the Home Office that in future bangers should contain gunpowder only as a bursting charge, and the quantity should not exceed 40 gr. (2.6 g.). This is a very much tamer article, in regard both to sound and to explosive force (Bennett, 1961). The effect of this policy has been dramatic in the prevention of blast injuries of the hands.

Burn and Blast Injury of the Face

This, the next commonest type of casualty, is usually caused by bending over a firework to light it, though the story given often states that the firework exploded prematurely, or that the child was puffing at the smouldering fuse to make it burn. The eyes are involved in a quarter to half the cases, with burning of the cornea or, less commonly, perforation of the eyeball. May (1956) circularized 70 hospitals with eye out-patient departments in London, and collected 14 major eye injuries due to fireworks on November 5, 1955. Nine people who received flash burns recovered, and one was left with an opaque cornea and vision limited to counting fingers; of the four injuries due to larger fragments of fireworks, two resulted in a blind eye, one in impaired vision, and one in recovery.

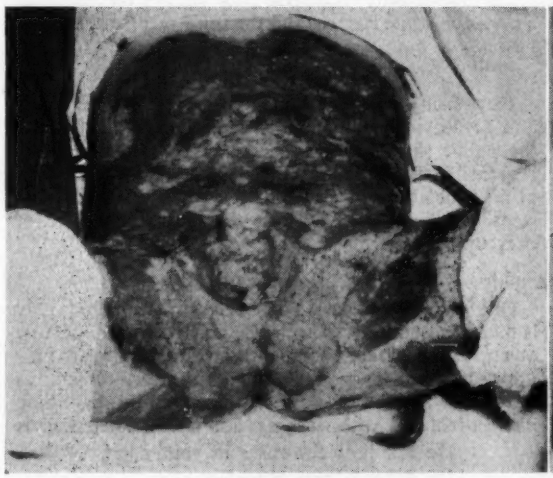


FIG. 1

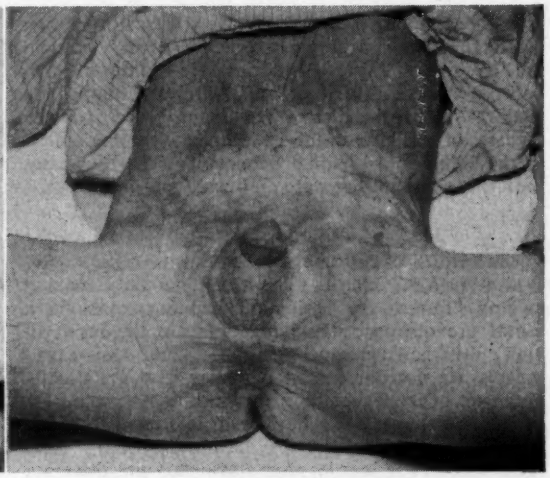


FIG. 2

A boy aged 5 was carrying a pocketful of rockets on November 5, 1956, when they exploded and he received 6% of deep burning (Fig. 1). This healed in two months after primary excision and grafting. A further graft was required in the left groin one year later to correct the contracture. He was finally discharged in April, 1960, with some skin shortage in the perineum but without symptoms (Fig. 2).

FIG. 3

FIG. 4

A boy aged 13 had a pocketful of fireworks on November 5, 1956, which he thought "were set alight by a spark." Six per cent. of deep burning on the thighs, groins, and left hand was excised the same evening and grafted five days later (Fig. 3). The burns were healed in two and a half months after three grafting operations. In the following year he had further grafts to both groins and his penis to correct skin shortage. He was discharged in October, 1958, symptom-free (Fig. 4).

Explosion in Trouser Pocket

The most extensive and deep burns are caused by fireworks exploding in a boy's trouser pocket. Usually this produces a deep burn, about the size of an outstretched hand, which requires excision and grafting and is followed by permanent scarring. Sometimes the clothes are set alight, and the whole leg, or the abdomen, genitalia, and opposite leg, are involved. One such burn in 1959 amounted to 17% of the body surface, and one in 1960 to 13%. It can be seen from Table I that 35 out of 48 burns of this type required skin grafts, most of them by primary excision and immediate grafting—an indication of the depth of these injuries. Two serious cases of this type are illustrated in Figs. 1–4.

Fireworks Lodging in Clothing

A further category is worth mention as being the second commonest cause of deep burns requiring grafting. This is a group in which fireworks lodge in the clothing. Typical histories are "firework fell between neck and coat collar," "firework jumped up leg," or "firework fell into Wellington boot." Of the 25 cases of this kind in this series, nine were due to fireworks falling into Wellington boots, and the four cases requiring skin grafting were all burns from this cause.

Other Causes

The incidence of some injuries due to other causes is also given in Table I. The hazards of throwing and kicking fireworks or letting off jumping squibs in a crowd are obvious: these practices are the result of high spirits and ignorance, or indiscipline. Mis-aimed rockets are not uncommon offenders, and are usually the result of inadequate preparation of a firm stand for firing. Fortunately few boys seem interested in seeing what makes the bang—or they have more sense. Bonfires cause fewer injuries than fireworks, and these are usually due to falling into them, lighting paper, or picking out hot objects.

Severity of Injuries

Table II gives an indication of the severity of the injuries, using 1960 as a sample year. The notes to the table correct any wrong impression which might be gained by using mean figures. The seven "fireworks in pocket" burns averaged 3% in extent, being mostly deep; one grafting operation, a month in hospital, and five out-patient visits for dressings were required before the burns were healed in about two months, with permanent scarring. There were four burns from fireworks in clothes and boots, about the size of the palm and partly deep; one required grafting and in-patient treatment for a fortnight, and the mean healing time for all was seven weeks, involving seven visits to hospital for dressings. The 34 injuries from other causes, excluding eyes, were less severe; on the whole they were small, relatively superficial, and did not require grafting, but the mean healing-time was a fortnight, involving three out-patient visits for dressings. There were seven eye cases associated on average with 1% of surrounding burn: two cases had conjunctivitis only, from superficial burning; two others had corneal abrasions, embedded foreign bodies, and some corneal opacity, but they were healed in 4 and 12 days without permanent disability. Three boys of 5, 12, and 15 years had hyphaemia and corneal abrasions; one was healed in 28 days but required capsulectomy six months later for a subluxated opaque lens; the second was left with an opaque white cornea, and the third recovered normal vision.

TABLE II.—*Severity of the Injuries* (1960)

	Firework in Pocket	Fireworks in Clothes or Boots	Other Firework Cases—Excluding Eyes	Eye Cases
No. of cases	7	4	34	7
Average area burned*	3%†	½%	½%	1%
,, full-thickness burn*	2%	½%	0§	—
,, No. of operations required	1	0‡	0	0
Average healing-time (days)	61	48	13	19
,, in-patient stay (days)	31	3	0	8
,, No. of out-patient visits	5	7	3	5

Note: Each case is recorded once, according to the principal injury or cause.
* 1% of the body surface is an area the size of the patient's outstretched hand.
† One of these 7 cases was 13% of the body surface.
‡ One of these 4 cases had 1 operation.
§ One of these 34 cases included ½% full-thickness burn.

How Long?

How many more of these anniversaries must come and go, leaving their mark on man, before doctors and the public show serious concern? As those who are responsible for repairing the damage, we see the size of the problem and its futility better than anyone. What steps can be taken to arrest this yearly epidemic of preventable suffering?

Education

One striking conclusion to be drawn from this study is that almost all these accidents arise from the deliberate or accidental misuse of fireworks. For some years now this has been appreciated by the press, which, as November 5 approaches, has co-operated by publishing interest features, with warnings and instructions, such as

Do not hold fireworks in your hand.

Do not put them in your pocket.

Do not bend over them to light them.

This is good advice. Doubtless it has reduced casualties among careful people, and one hopes this prophylactic will continue. But no decline in casualties is noticeable from year to year. Slogans and good advice are not reducing the problem.

Young children have no knowledge of the dangers of fireworks, just as they have no road sense. Labelled instructions cannot be read in the dark, and are often not read in the best light. While fireworks can be obtained by children the task that confronts us is to reach parents who have an antipathy to instruction and to persuade them to train their children in handling explosives. No gift of clairvoyance is required to see that if we depend on education for improvement this problem will still be with us in fifty years.

Restriction

Organized displays, and private parties organized by adults who know the dangers, are a safe form of entertainment. This firm impression is supported by our findings. For example, of the 34 casualties in 1949, 19 were serious enough for follow-up: 18 of these 19 were not in any supervised party; one was with his own parents in the garden.

This raises the possibility of achieving safety by restricting fireworks to organized displays. Restriction would be no novelty, for, as Brock (1950) points out,

"An act of William III made fireworks illegal; the penalty for manufacture or selling was five pounds, and for letting them off, whether on one's own premises or in a public place, was 20 shillings or one month's hard labour": but this legislation failed to control the industry. There is already a restriction on those allowed to buy fireworks—they must not be under 13 years of age; but in practice this regulation is ineffective because it is impossible to enforce in the face of connivance by parents and older boys. The effectiveness of controlling fireworks at the source—that is, at the factory—is clearly shown by the immediate and lasting reduction in blast injuries of the hands since production of the thunderflash was stopped.

The suggestion of legal enforcement does not imply callousness on the part of the trade: the contrary, in fact, is true. From time to time leading manufacturers have agreed among themselves to ban popular types of fireworks which have proved hazardous. For instance, air-bomb types which were produced for some years between the wars have been discontinued; rockets on sale to the general public are limited to the five-shilling size to prevent danger from fall-out of unduly large sticks; and twelve months ago it was decided to discontinue production of aerial torpedo types which fly about in an unpredictable manner (Bennett, 1961).

Substitution

Opposition to change in the field of preventing accidents comes commonly from vested interests, but in this case there is no need to change general custom or spoil sport or restrict production.

Fireworks have been displayed at spas and pleasure gardens under private enterprise since the middle of the eighteenth century: those of C. T. Brock at the Crystal Palace in London from 1865 to 1935 were perhaps the best known. Only a few years ago I attended a crowded privately organized display in a meadow at Tewkesbury, with the Abbey as the scenic backcloth—a perfect, natural setting. This seemed quite to steal the thunder from anything a few boys could put up. It was attended by the public, and, with money raised by the small individual admission fee, sufficient high-quality fireworks were displayed to make a most successful evening—and one which was both safe and, I feel sure, without loss to the manufacturers. With encouragement, local displays of this type could replace the precocious handling of explosives by children. How to develop this substitution profitably is surely a challenge to the trade as a whole.

Conclusion

On the evidence of recent data about firework injuries treated at the Birmingham Accident Hospital, a serious proposition is put forward to reduce the disgraceful and unnecessary suffering of the Guy Fawkes celebration year after year.

This proposition combines legal restriction with an opportunity for the industry to take the initiative in reorganizing the distribution of their products.

Legislation is called for to prohibit the retail distribution of fireworks except for organized displays—nothing less will prevent these injuries.

As a substitute, safe organized displays might well be encouraged for public enjoyment and the welfare of the industry.

I am grateful to my colleague, Mr. J. S. Cason, and to Mr. P. Jameson Evans of the Midland Eye Hospital, for allowing me to use their cases, and to Mr. William Gissane and Dr. John Bull for their interest in this problem which has been a stimulus through the years.

References

Bennett, T. M. (1961). Personal communication.
Brock, A. St. H. (1950). *Chambers's Encyclopaedia*, **11**, 391.
May, W. (1956). *Brit. med. J.*, **2**, 1039.
Wiseman, R. (1705). *Eight Chirurgical Treatises*, 4th ed., p. 416. Printed for Benjamin Tooke.

PULMONARY AGENESIS

BY

H. EVERLEY JONES, O.B.E., M.B., F.R.C.P.

AND

C. H. L. HOWELLS, M.D., B.Sc.

The Royal Hospital, Wolverhampton

The congenital absence of a lung or part of a lung is always a surprising finding and is something of a rarity. Burger (1947) collected 54 cases and Wexels (1951) recorded 87. Oyamada *et al.* (1953), in an exhaustive review of the literature, were able to find 73 cases of absent lung and 38 cases of hypoplasia. In 1955 Hochberg and Naclerio reviewed 100 cases and stated that they could find "less than 150 cases reported in the medical journals." Single cases have been reported from time to time in the American literature, notably by Warner *et al.* (1955) and Steiner (1956).

A further case came to necropsy here recently and was accompanied by a number of other defects. The fact that three other examples were treated in one general hospital in the past four years suggests that the condition may not in fact be so rare as has been thought.

Case 1

This patient, the first child of healthy parents, was born normally at home. Regular respirations were established 10 minutes after birth, but breathing was wheezy and a good deal of mucus was produced. A cyanotic attack occurred seven hours later and was terminated by aspiration of the pharynx. He was brought to hospital when 11 hours old. On admission the temperature was 90° F. (32.2° C.) and respiration rate 68 a minute. His colour was normal except for the extremities, which were cold and cyanosed. The right thumb was small and was attached to the hand by a tag of skin. It was noticed that the anus was imperforate and no dimple was seen. An unusually large median raphe extended from the anal region forward along the midline of the scrotum and penis.

Examination of the chest revealed that the left hemithorax was a little fuller than the right. The trachea was deviated to the right and the heart apex beat was behind the sternum. The heart sounds were most clearly heard on the right side of the chest. The percussion note was impaired and the breath sounds were diminished on the right side, while rales were heard, chiefly on the left side. The rest of the physical examination was normal and a catheter was passed into the stomach without difficulty.

X-ray examination of the chest showed the heart to be in the right hemithorax and there was no evidence of a right lung (Fig. 1). *X*-ray examination of the abdomen with the child inverted demonstrated the presence of air within a short distance of the perineum. Within a few hours a blackening appeared at the perineal end of the raphe. This spread steadily forwards across the scrotum and to the end of the prepuce. It was presumed to be meconium.

Thirty-six hours after admission operation was performed. The rectum was demonstrated ½ in. (1.3 cm.) below the perineal skin. The rectum was identified and the rectal mucosa was sewn to the perianal skin.

On the third day small amounts of meconium were passed and urine was passed once, but the abdomen soon became distended and coils of intestine were visible. Partial relief followed passage of a rectal tube. From this time onwards great difficulty was experienced in evacuating the bowels.

FIG. 1.—Case 1. Radiograph of chest in life. The heart is in the right hemithorax.

Frequent use of the rectal tube with small saline washouts and the instillation of detergent kept the distension within bounds until shortly before death.

On the fifth day the bladder was palpably distended and no further urine had been passed. A urethral catheter could not be passed even under an anaesthetic, there being an apparent obstruction at the internal sphincter. Suprapubic catheterization was therefore performed, and was maintained until the 23rd day, when urine was passed normally through the urethra.

On the 12th day the left kidney was thought to be palpably enlarged and the urine was found to be infected with *Escherichia coli*. This infection was treated with nitrofurantoin ("furadantin"), to which the organism was sensitive. The infection was never completely controlled despite changes in treatment. The blood urea rose from 86 mg./100 ml. on the 12th day to 380 mg./100 ml. shortly before death.

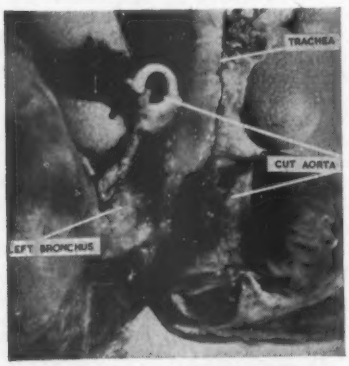


FIG. 2.—Case 1. Post-mortem photograph showing single bronchus. There is no trace of the right bronchus or right lung.

During the third week a systolic murmur, most pronounced at the base, was just audible. It later became more noticeable. By the 50th day severe distension and palpable faeces suggested intestinal obstruction. *X*-ray examination of the abdomen at this time showed gross distension of the colon with faecal masses. Colostomy was considered, but prior to operation a micturating cystogram was taken on the 52nd day. This revealed a large left-sided hydronephrosis and megaureter without evidence of any kidney or ureter on the right side. On the 53rd day the infant suddenly collapsed and died.

Post-mortem Findings.—The body was that of an undersized wizened infant. The right thumb was attached by a thin fold of skin. On opening the thoracic cavity the heart was seen to be in the right side of the chest. Further investigation revealed that the right lung was completely absent and the apparent dextrocardia was due to mediastinal shift. The heart itself was normal. Further dissection revealed that the trachea led directly into the left main bronchus (Fig. 2). There was no attempt at formation of a right bronchus. The right kidney was absent and the left greatly hypertrophied. The whole of the pelvic colon was ballooned. Histological evidence of Hirschsprung's disease was not found.

Case 2

This patient was the second child of healthy unrelated parents, the other child, 2½ years older, being normal. Pregnancy was uneventful and he was delivered normally at term; birth weight 7½ lb. (3,400 g.). He was a little slow to breathe and was noticed to have a short, thick neck. He soon settled and throve on the breast without respiratory symptoms until he was nearly 3 months old, when he was sent to hospital. This was necessitated by the occurrence of cyanosis and grunting respirations 10 minutes after the evening feed.

Examination revealed a greyish cyanosed infant, weighing 10 lb. (4,535 g.). His temperature was 99° F. (37.2° C.), pulse 156, and respirations 66. The neck was short, with a bony projection in the midline posteriorly and a small dimple at the summit. The right side of the chest was prominent and the left flattened, with very little movement on respiration. The percussion note was dull and breath sounds were diminished on the left side. The heart apex beat was not felt, but there was a systolic murmur at the base.

X-ray examination of the chest showed displacement of the heart and mediastinum to the left, with the heart in the left hemithorax. The right lung was normal. *X*-ray examination of the spine revealed multiple vertebral abnormalities in the cervico-dorsal region. Bronchoscopy showed a trachea of normal dimensions with inflamed mucosa at the lower end. Only one main bronchus (the right) was seen. A bronchogram revealed a normal right bronchial tree, but there was no filling on the left.

The child was nursed in oxygen and given penicillin and streptomycin. The cyanosis and respiratory distress slowly improved and oxygen was discontinued after a week. At this time the pulmonary signs were unchanged, but the murmur had become continuous and was best heard posteriorly over the upper left chest.

Since discharge from hospital he has become progressively more cyanosed and dyspnoeic on exertion. Clubbing of the fingers developed. At the age of 2 years the continuous murmur was still present and the second heart sound was loud and single. Venous angiography at this age showed the presence of a single ventricle and common truncus.

Case 3

This patient, the ninth child of healthy unrelated parents, was born normally at term after an uneventful pregnancy and labour. Weight at birth was 7 lb. 2 oz. (3,230 g.). All his siblings are healthy. He was breast-fed from birth until he was first seen as an emergency admission to hospitals at the age of 3 months. He had always had some cough and wheezing, but on the day of admission, shortly after a feed, he became very dyspnoeic and cyanosed. He then experienced generalized convulsive movements and was brought to hospital.

By the time he had reached the ward the convulsion had ceased and he was no longer cyanosed. His temperature

was 99° F. (37.2° C.), pulse 166, and respirations 48. The head—circumference 16½ in. (41 cm.)—seemed large in proportion to the trunk, the chest circumference being 14½ in. (36.7 cm.). His weight was 9 lb. 14 oz. (4.480 g.). Accessory auricles were present on both sides. The neck was short. An inspiratory wheeze was audible and the chest was asymmetrical, with prominence of the left side and flattening of the right. The trachea was displaced to the right and there was dullness and reduced air entry on this side. No area of cardiac dullness was noted on the left side, but the heart sounds were normal. *X*-ray examination showed the heart to be displaced into the right side of the chest. The right hemithorax was smaller than the left and no lung markings were seen on that side except for an apparent herniation of the left lung across the midline.

Bronchoscopy revealed a small slit-like trachea, and the left main bronchus was the only main bronchus visible. Bronchography showed the presence of opaque material in the left main bronchus, but no evidence of a right main bronchus was seen. The branches of the left main bronchus were poorly defined.

From this time onwards he was rarely out of hospital and was treated repeatedly for respiratory infections. He gained weight slowly, and at the age of 11 months weighed 15¼ lb. (6,915 g.). His mental development approximated that of a 3-months-old baby. At this age a further bronchogram was made with the object of delineating more clearly the subdivisions of the left main bronchus. He died suddenly just after the procedure was finished.

Post-mortem Examination.—Both the right lung and the upper lobe of the left lung were absent. There was no trace of the right main bronchus. In addition there were horseshoe kidneys, vertebral defects in the cervical and thoracic spine, and accessory auricles.

Case 4

This patient, the only child of healthy unrelated parents, was born normally after an uneventful pregnancy, with a birth weight of 7½ lb. (3.290 g.). She was breast-fed for five months, and weaned without difficulty. Since the age of 4 months she had suffered from attacks of cough and wheezing, and a rattle in the throat caused some concern to the parents. She was admitted to hospital at the age of 9 months. Her weight was 15 lb. 14 oz. (7,200 g.). Her temperature was 99° F. (37.2° C.), pulse 130, and respirations 50. Abnormal findings were confined to the chest, and consisted of slight diminution of the size of the right hemithorax with partial absence of the right pectoralis major muscle. The heart and trachea were deviated to the right. The percussion note was impaired on the right side and breath sounds were feeble on that side.

X-ray examination of the chest suggested collapse of the right lung with displacement of the mediastinum to the right and herniation of part of the left lung across the mediastinum. The tuberculin test (1:1,000) was negative. Bronchoscopy revealed a very small right bronchial tree and no upper- or middle-lobe orifices were seen. A bronchogram confirmed the absence of the right upper- and middle-lobe bronchi. The remaining bronchial components filled normally.

Since that time she has developed normally and the signs have remained unchanged except that a grade 2 systolic murmur has appeared. The cough and wheezing have diminished and are only noticeable with winter colds. At the age of 4½ she was 44 in. (112 cm.) tall and weighed 38 lb. (17.2 kg.), and her intelligence seemed normal. She has undergone recent Mantoux conversion without any changes in the chest *x*-ray picture.

Discussion

The condition described is one of unknown aetiology. Whatever the precise cause may be, presumably there must have been interference early in the development of the embryo. Even at the 3-mm. stage lung buds can be detected as outgrowths from the trachea (Baxter, 1953), and it may be of significance with reference to Case 1 that the mesonephros also begins to form at this time. The nature of the interference remains a mystery. Familial incidence is noticeably absent, while in none of the cases described was there any history of virus infection, *x*-ray exposure, or trauma.

Although lobar agenesis is comparatively uncommon and in most cases the lung is completely absent, the amount of surviving lung tissue varies. Schneider (1912) drew attention to this variation and suggested a classification. He divided the cases into three groups: (1) those with no trace of bronchus, vascular supply, or lung on the affected side; (2) those in which there was a demonstrable bronchial remnant; and (3) those in which the bronchus was slightly more developed, lay within the mediastinum, and ended in a fleshy structure without lobes.

When such a large amount of pulmonary tissue is absent it seems somewhat surprising at first sight that difficulties in diagnosis occur. In infants, however, although there is often fullness of the opposite hemithorax, the mediastinal displacement may pass unnoticed, since even in health the apex beat is often impalpable. A cardiac bruit is not uncommon and may be due either to increased blood-flow through a single pulmonary artery or to concomitant congenital heart disease. The latter is a frequent accompaniment, and was found in 23 of the 73 cases collected by Oyamada *et al.* (1953). Other congenital abnormalities, too, commonly coexist, and it is often these rather than any pulmonary maldevelopment that lead to the death of the patient (Case 1). Indeed, death from respiratory insufficiency is by no means invariable. Some patients have reached an advanced age without difficulty, and it seems likely that respiratory distress is precipitated by intercurrent infection.

In the differential diagnosis in infancy, diaphragmatic hernia, pneumothorax (especially associated with staphylococcal pneumonia), lobar emphysema, and dextrocardia need consideration. The clinical characteristics of these conditions are well known and the increasingly grave symptoms caused by the first three will usually lead to their detection.

Summary

Four further cases of pulmonary agenesis are described and the literature is briefly reviewed. The coexistence of other congenital abnormalities is mentioned and their role in causing death emphasized.

We thank Dr. A. P. Booth for the *x*-ray work in his department; also Mr. E. G. Dolton for bronchoscopy, surgical advice, and treatment.

References

Baxter, J. S. (1953). *Frazer's Manual of Embryology*, 3rd ed. Baillière, Tindall and Cox, London.
Burger, R. A. (1947). *Amer. J. Dis. Child.*, **73**, 481.
Hochberg, L. A., and Naclerio, E. A. (1955). *Dis. Chest*, **28**, 275.
Oyamada, A., Gasul, B. M., and Holinger, P. H. (1953). *Amer. J. Dis. Child.*, **85** 182.
Schneider, P. (1912), in E. Schwalbe's *Die Morphologie der Missbildungen des Menschen und der Tiere*, **3**, pt. 2, 772. G. Fischer, Jena.
Steiner, H. A. (1956). *Radiology*, **67**, 751.
Warner, A. L., Palladino, N. M., Schwartz, W., and Schuster, A. (1955). *J. Pediat.*, **46**, 200.
Wexels, P. (1951). *Thorax*, **6**, 171.

HYPOPITUITARISM ASSOCIATED WITH INTRACRANIAL ANEURYSMS

BY

W. VAN 'T HOFF, M.A., M.B., B.Chir., M.R.C.P.
Senior Medical Registrar, Westminster Hospital

R. W. HORNABROOK, M.D., M.R.A.C.P.
Lately Resident Medical Officer, National Hospital, Queen Square

AND

VINCENT MARKS, M.A., B.M., M.R.C.P.Ed.
Senior Lecturer in Chemical Pathology, Institute of Neurology, National Hospital, Queen Square

Intracranial aneurysms may present as an acute emergency, with subarachnoid or intracerebral haemorrhage. Loss or disturbance of consciousness is usual, with neck rigidity and a blood-stained cerebrospinal fluid. On the other hand, the clinical presentation may be one of compression of the oculomotor nerves, optic nerve or chiasm, without blood leakage, and in these cases the gradual evolution of an ocular palsy or visual failure may cause considerable difficulty in diagnosis, in particular from basal intracranial tumours such as meningiomas. Compression of the optic nerve or chiasm is by no means an unusual event, and in this case an aneurysm may mimic the effects of a pituitary tumour or a meningioma. The absence of signs of endocrine dysfunction is usually regarded as an important feature in distinguishing aneurysms and meningiomas from pituitary tumours, and there is no doubt that in general this holds good.

The rarity of endocrine features in patients with basal intracranial aneurysms has encouraged us to present these three cases of intracranial aneurysm, all of which had evidence of hypopituitarism.

Methods

Serum electrolyte, urea, and cholesterol concentrations were estimated by the usual routine methods. Blood sugar was measured in capillary blood by the method of Hagedorn and Jensen (1923) and blood glucose by glucose oxidase (Marks, 1959). The glucose-tolerance test was performed after the ingestion of 50 g. of glucose. Urinary 17-ketosteroids were estimated by the method of Norymberski *et al.* (1953), and 17-hydroxycorticosteroids by the method of Appleby *et al.* (1955) with minor modifications in the dilutions of some of the solutions used. Urinary steroids were measured before and after an infusion of 25 units of adrenocorticotrophin given over eight hours on two successive days, as described by Jenkins *et al.* (1955). Urinary gonadotrophin excretion was assayed according to the method of Loraine and Brown (1959).

The basal metabolic rates were measured by the method of Du Bois and Du Bois (1916), using the normal standards of Boothby and Sandiford (1929). In Cases 1 and 3 the uptake by the thyroid gland was measured with a scintillation counter four hours after an oral dose of 30 μc of ^{131}I and expressed as a percentage of the dose given. In Case 2 the "T" test of Fraser *et al.* (1953) was employed.

The results of the laboratory investigations of the three patients are summarized in the accompanying Table.

Case 1

A spinster aged 32 was admitted to the Westminster Hospital on February 9, 1959, under the care of Dr. S. P. Meadows for assessment. She was quite normal as a child and the menarche occurred at the age of 14. Her periods were scanty but regular until they stopped suddenly at the age of 19. Three years later, in 1948, she happened to cover the right eye and discovered that she was only just able to perceive light with the left eye. She remained well otherwise until 1950, when she suddenly developed a severe occipital headache associated with vomiting. Vision in the right eye deteriorated rapidly, and when she was admitted to the Queen Elizabeth Hospital, Birmingham, under the care of Mr. J. M. Small, a week later, she was blind in both eyes. She had optic atrophy on the left and right-sided papilloedema. There was weakness of the left fourth and sixth cranial nerves, and she had complete third and fourth cranial nerve palsies on the right side. She was extremely pale, but there were no other general signs. Radiographs of the skull at that time showed a considerably expanded sella turcica, with backward angulation and erosion of the dorsum sellae. Carotid angiography showed a very large left-sided carotid aneurysm with a concave lower margin, situated above the sella. The left common carotid artery was ligated on February 7, 1950, and the left internal carotid ten days later. After this she developed temporary hyperpyrexia and vomiting, which persisted intermittently for about two years. Headaches lasted about one year. She spent four months in hospital and a further two years in bed at home before her strength slowly improved.

Results of Investigations in Three Patients with Intracranial Aneurysms and Clinical Hypopituitarism

	Case 1	Case 2	Case 3
Haemoglobin (100%=14·8 g./100 ml.)	89%	90%	75%
Serum sodium (mEq/l.)	142	130	140
,, chloride ,,	103	105	94
,, potassium ,,	3·6	4·6	4·6
,, urea (mg./100 ml.)	23	28	42
,, cholesterol (mg./100 ml.)	364	230	212
Glucose tolerance test (blood sugar in mg./100 ml.):			
Fasting	82	112	—
30 min. after glucose	126	187	—
60 ,, ,, ,,	68	—	—
90 ,, ,, ,,	84	187	—
120 ,, ,, ,,	90	175	—
180 ,, ,, ,,	—	162	—
Urinary 17-hydroxycorticosteroids (mg./24 hours):			
Day 1	1·5	6·5	2·6
,, 2	2·6	5·5	3·6
,, 3 A.C.T.H., 25 units i.v.	5·8	19·0	17·0
,, 4 ,, ,, ,, ,,	12·0	35·0	28·0
Urinary 17-ketosteroids (mg./24 hours):			
Day 1	1·0	20·0	5·0
,, 2	1·0	17·0	3·8
,, 3 A.C.T.H., 25 units i.v.	1·7	22·0	5·8
,, 4 ,, ,, ,, ,,	2·3	28·0	9·6
Water load in ml.	1,000	1,500	—
% of water load excreted in 4 hours:			
Without cortisone	25%	15%	
After ,,	161%	65%	
Urinary gonadotrophin excretion in 24 hours	<6 mg. (H.M.G.)	—	—
Basal metabolic rate	−20%	−6%	—
^{131}I uptake of thyroid as % of administered dose (normal, 15–35%)	22%	—	4%
^{131}I urine excretion as % of administered dose:			
0–8 hours	—	33·0	—
8–24 ,,	—	16·4	—
24–48 ,,	—	2·5	—
	Total "T" value	51·9 3·9	

At the time of her admission to Westminster Hospital she looked younger than her age, and was a striking picture of hypopituitarism (Fig. 1). She was very pale, with smooth skin and fine scalp hair. Her breasts were underdeveloped, and pubic and axillary hair was absent.

She was quite blind in both eyes and there was bilateral optic atrophy. There was slight impairment of elevation of both eyes, and nystagmoid jerks occurred on lateral deviation to both sides. No other abnormal signs were observed, and her blood pressure was 120/80 mm. Hg.

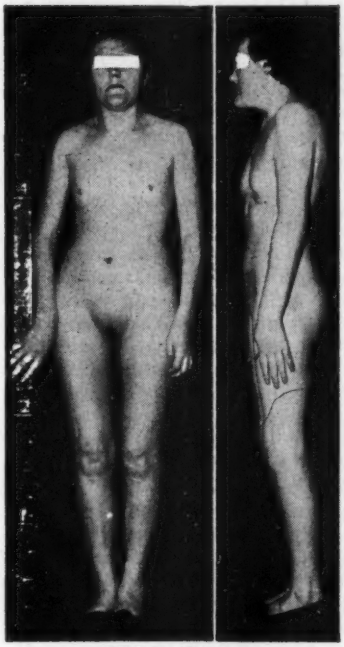


FIG. 1.—Case 1.

Radiographs of the skull showed that the sella turcica had increased in size since 1950; the anterior clinoid processes were blunted, and the dorsum sellae had now disappeared.

Urinary gonadotrophin excretion was reduced, and there was evidence of adrenal and thyroid hypofunction (see Table). Treatment was started with cortisone 25 mg. and thyroid 1 gr. (65 mg.) daily, and testosterone isobutyrate by intramuscular injection 100 mg. monthly; there was a dramatic improvement in her general condition. When last seen, on December 7, 1960, she continued to feel very well, and had started training for a job, which she had not felt well enough to do previously.

Case Report Summary.—A 32-year-old woman first noticed impairment of vision in one eye nine years previously. Two years after this she suddenly lost the sight in both eyes, at which time radiographs of her skull showed a considerably expanded sella turcica. Carotid arteriography revealed a very large left carotid aneurysm above the sella turcica, and the left common and, a few days later, the left internal carotid artery were ligated. She was severely ill, and spent two years in bed. At the time of her present admission she was quite blind and was found to have severe hypopituitarism. There was a marked improvement in her general condition after endocrine therapy.

Case 2

A single man aged 54 was referred to the out-patient department of the National Hospital on August 6, 1958, because of an attack of vertigo and vomiting. He was found to have nystagmus, and his urine contained a large amount of glucose. While awaiting admission for investigation he was referred to the West Middlesex Hospital under the care of Dr. Q. J. C. Hobson for control of his glycosuria. It was then noted that his appearance was suggestive of hypopituitarism, and a radiograph of his skull showed gross destruction of the pituitary fossa.

His haemoglobin was 101%, and two random blood-sugar concentrations were 298 and 296 mg. per 100 ml. Diabetes mellitus was diagnosed, and controlled on a 2,500-calorie diet and tolbutamide 1 g. three times a day. During the next few months he gradually reduced the dose of tolbutamide on his own accord without ill effects, and when readmitted to the West Middlesex Hospital in January, 1959, he had stopped taking it altogether. His appearance and general condition were unchanged. Fasting blood-sugar was normal, but he had a diabetic glucose-tolerance curve. A 48-hour radioiodine excretion test was within normal limits (see Table).

On January 17, 1959, he was transferred to the National Hospital under the care of Dr. John Marshall for further investigation. He had no headaches or visual disturbances, and he denied any change in his appearance, which on admission was typical of hypopituitarism. Libido had always been absent. Body hair was scanty and the pubic hair was feminine in distribution. The testicles were small and soft, and the blood-pressure was 135/80 mm. Hg. There were no other abnormal signs in the nervous or other systems. In particular, the visual fields were full.

Radiographs of the skull showed marked decalcification and erosion of the dorsum sellae, the floor of the pituitary fossa, and the walls of the sphenoidal air sinus. There was also erosion of the right anterior clinoid process and enlargement of the superior orbital fissure on that side. On lateral view a few flecks of calcification were seen overlying the fossa. A right carotid arteriogram demonstrated an aneurysm of the right carotid artery, roughly spherical and about 2 cm. in diameter, the origin of which was 2 or 3 cm. behind the cavernous sinus. A lumbar air encephalogram demonstrated a suprasellar mass. Headache, nausea, and vomiting were more severe than usual after this procedure, but were rapidly relieved on infusion of adrenocorticotrophin.

The haemoglobin was 90% and the white blood count was normal. Cerebrospinal fluid was clear and colourless, and contained one white cell per c.mm., 120 mg. protein per 100 ml., and the Lange curve was 0002221000. The W.R. was negative.

His urine was normal and sugar-free on admission, but he developed marked glycosuria following the infusion of adrenocorticotrophin, which diminished only gradually over the next few days. Urinary 17-ketosteroid excretion was within normal limits, but 17-hydroxycorticosteroid excretion was at the lower limits of normal. Both rose after the administration of adrenocorticotrophin. Diuresis of a water load, however, was greatly diminished, and was only partially improved by cortisone (see Table).

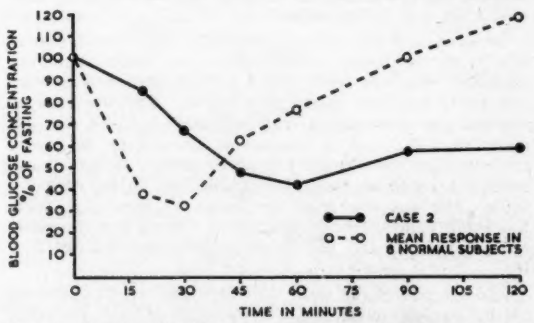


FIG. 2.—Case 2. Insulin-tolerance test. Insulin 0.1 unit per kg. body weight injected intravenously at 0 min.

An intravenous glucose-tolerance test showed an elevated fasting blood glucose and a delayed disappearance. An insulin-tolerance test showed a delayed response to insulin, with hypoglycaemic unresponsiveness (Fig. 2).

In view of the absence of neurological involvement it was thought that surgical interference was not justified, but that he should be kept under close observation. He remained

well when last heard of in December, 1960, and required no substitution therapy for his hypopituitarism, nor any hypoglycaemic agents.

Case Report Summary.—A 54-year-old man was found to have mild diabetes mellitus, which responded to oral hypoglycaemic agents. In the ensuing months his diabetes improved spontaneously, and he was found to have mild hypopituitarism. After the administration of adrenocorticotrophin glycosuria recurred. Radiographs of his skull showed enlargement of the sella turcica, and an arteriogram revealed an aneurysm of the right internal carotid artery in the region of the sella.

Case 3

A married woman aged 63 was admitted to the Westminster Hospital on July 29, 1958, under the care of Dr. S. P. Meadows for investigation of visual failure and a persistent pyrexia. As a girl she had bitemporal migrainous headaches with nausea but no visual disturbances. In September, 1956, she suddenly noticed a noise like a waterfall in the left side of her head, after which she was unconscious for four days. There was proof of a subarachnoid haemorrhage, and subsequently carotid arteriography at another hospital was said to have shown an aneurysm of the anterior communicating artery. She recovered from the subarachnoid haemorrhage but did not feel quite as fit as previously. In September, 1957, she began to complain of nausea and frequent vomiting after food. This was associated with general malaise, lethargy, and anorexia, and she lost about three stone (19 kg.) in weight. After a tentative diagnosis of myelomatosis, later not confirmed, she received a short course of prednisone, during which time she felt better.

In December, 1957, she noticed the gradual onset of visual failure, first in the right and then in the left eye. This progressed until at the time of admission she was only able to see objects a few feet in front of her. She also developed frequent severe bilateral headaches, severe anorexia, and intolerance to cold. Shortly before her admission to the Westminster Hospital she developed an intermittent pyrexia, with increasing malaise, but no localizing features apart from headaches and failing vision.

On admission she was an ill-looking white-haired woman who preferred to lie curled up in bed under numerous blankets. She was pale, with a smooth skin, and axillary and pubic hair was moderately sparse. She was slow to respond and co-operated with difficulty, but she was not confused. She had a bitemporal visual-field defect on confrontation; she could just count fingers in both nasal fields, but could see hand movements only in the temporal fields. She was unable to see Jaeger test type 20. There was slight pallor of both optic disks. There were no other abnormal signs, and her blood-pressure was 150/90 mm. Hg.

Radiographs of the skull showed slight loss of definition of the dorsum sellae and the posterior clinoid processes. Carotid arteriography showed a large lobulated aneurysm in the region of the anterior communicating artery, which filled from the left side.

The four-hour radioiodine uptake of the thyroid gland and urinary steroid excretion were both reduced (see Table). Urinary gonadotrophin excretion was not measured, and she was unable to co-operate sufficiently for her basal metabolic rate to be measured. Her haemoglobin was 87%, and her urine contained a trace of protein.

Treatment was started with cortisone 25 mg. daily, and four days later thyroid was added, working up gradually to 1½ gr. (100 mg.) daily. There was a dramatic improvement in her general condition, and when she left hospital four weeks after starting treatment she was up all day, cheerful and taking an interest in her surroundings. Her visual acuity improved, and on September 15, 1958, it was 1/60 on the left and 6/60 on the right, but her bitemporal hemianopia was still present. She has not been seen again, as she lives in Jersey, but her doctor wrote on December 9, 1960, saying that she had kept well until August, 1960, when she developed a left hemiparesis, since when she has been more or less confined to bed.

Case Report Summary.—A 63-year-old woman had had a subarachnoid haemorrhage two years before we saw her and was found to have an anterior communicating aneurysm. At the time of her present admission she had visual failure and hypopituitarism. Radiographs of her skull showed loss of definition of the posterior clinoid processes, and carotid arteriography revealed an aneurysm in the region of the dorsum sellae. After endocrine therapy there was a marked improvement in her general condition and some increase in her visual acuity.

Discussion

Clinical evidence of pituitary dysfunction is generally thought to be rare in patients with basal intracranial aneurysms (Meadows, 1951). McDonald and Korb (1939), in reviewing the symptomatology of over 1,000 cases, do not mention the occurrence of endocrine abnormalities; and aneurysms were not described as a cause of hypopituitarism in the review by Sheehan and Summers (1949). Hamby (1952) in his treatise on intracranial aneurysms mentions only briefly the possibility of hypothalamic damage by an aneurysm.

On the other hand, in patients with pituitary tumours signs of abnormal pituitary function are common. Antony Jefferson (1957) observed features of hypopituitarism in 66% of males and 37% of females in a series of 135 patients with chromophobe adenomas or craniopharyngiomas. Weinberger *et al.* (1940) considered the absence of endocrine symptoms an important diagnostic feature in differentiating aneurysms at the base of the brain from pituitary adenomas.

Although its true nature was unrecognized at the time, pituitary dysfunction associated with an intracranial aneurysm was probably first described by Bramwell (1887). The patient was a 31-year-old man with blindness, mania, scanty pubic and facial hair, testicular atrophy and gynaecomastia, in whom a huge carotid aneurysm was an unexpected finding at necropsy. The aneurysm had eroded the sella turcica, but Bramwell does not comment on the state of the pituitary gland. There was considerable softening of the base of the brain.

Few published accounts of well-documented pituitary dysfunction with basal intracranial aneurysms have appeared in the 75 years since Bramwell's paper. Patients in whom hypopituitary features predominated have been described by Lodge *et al.* (1927), Sjöqvist (1936), Jefferson (1937), Werner *et al.* (1941), Escamilla and Lisser (1942), Mecklin (1950), Schiefer and Marguth (1956), Höök and Norlén (1958), and van Staveren and Smits (1959). In most of these cases few endocrine details are available, but Driesen (1959) has described a girl of 16 years who was small and sexually underdeveloped, with well-documented hypopituitarism, and in whom an intrasellar aneurysm was successfully clipped. White and Ballantine (1961) also confirmed the diagnosis of hypopituitarism by endocrine investigations in a woman of 61, thought at first to have a chromophobe adenoma. She was later found to have an intracranial aneurysm and subsequently died. Unfortunately the necropsy report does not mention the condition of the hypothalamus or the pituitary gland.

Another case was reported by Gallagher *et al.* (1956), who described the case of a woman of 54 who was admitted to hospital with the complaint of headache. During the previous year she had also complained of polyuria and urinary frequency. She appeared ill and looked older than her years. Following an arteriogram, which demonstrated a huge aneurysm arising from the carotid artery at its bifurcation into the middle and anterior cerebral arteries, she collapsed and the blood pressure fell to 80/60 mm. Hg. Intravenous noradrenaline was given with minimal effect, but she recovered when steroid therapy was instituted. The results of subsequent laboratory investigations confirmed the clinical impression of panhypopituitarism.

The intolerance to traumatic procedures such as air-encephalography, arteriography, or craniotomy by patients with pituitary tumours is well known (Jefferson, 1957). It is salutary to remember that a similar intolerance can occur with intracranial aneurysms as in Case 2 and in the patient described by Gallagher *et al.* Presumably in each case the cause is impaired hydrocortisone secretion.

The pathogenesis of pituitary dysfunction occurring with basal intracranial aneurysms is uncertain. In the patient described by Lodge *et al.* (1927) the anterior pituitary was congested but otherwise normal at necropsy, but there was much softening of adjacent brain tissue where the aneurysm had projected into the base of the brain. Gallagher *et al.* (1956) ascribed hypopituitarism in their patient to pituitary atrophy from compression by the aneurysm acting as a large suprasellar space-occupying lesion.

This theory is unsatisfactory for several reasons. In the first place, endocrine abnormalities are rare in patients with intracranial aneurysms, including those which can be demonstrated, either surgically or radiologically, to fill the whole of an expanded sella turcica (Zollinger and Cutler, 1933; Schiefer and Marguth, 1956; Rhonheimer, 1959). Secondly, the occurrence of hypopituitarism bears little or no relationship to the size of the aneurysmal sac. The largest carotid aneurysm seen personally (R.W.H. and V.M.) was in a young woman who had borne a child six months earlier. Finally, signs of pituitary dysfunction are occasionally those, not of hypopituitarism, but of acromegaly (Bozzoli, 1937; Girard *et al.*, 1953; Brouwer, 1949; Offret and Aron, 1959), or of Cushing's syndrome (Höök and Norlén, 1958).

It seems likely that these diverse manifestations of endocrine dysfunction may be due to interference with the blood-supply of the hypothalamic nuclei, which are now believed to regulate the secretion of the pituitary hormones, since neither acromegaly nor Cushing's syndrome is attributable to damage to the anterior pituitary gland directly. Luft (1958), in discussing Höök and Norlén's patients, mentioned that atrophy of the paraventricular nucleus had been described in Cushing's syndrome. Complex endocrine changes ranging from panhypopituitarism to precocious puberty have also been described in lesions of the hypothalamus with an anatomically intact pituitary gland (Bauer, 1954). The exact abnormality probably depends upon the particular regulatory centres affected.

The vagaries of the vascular supply to the neural structures in the hypothalamus and base of the brain have been described by Dawson (1958). He found that normally each of the hypothalamic nuclei obtained its blood-supply from more than one vessel, but that the size of the vessels varied enormously in different subjects. Presumably in most cases of aneurysm there is interference with the blood-flow through some of the small arteries arising from the affected vessel. Only in those cases where the alternative blood-supply is inadequate would atrophy in the hypothalamic nuclei be expected to occur.

The possibility of endocrine dysfunction in a patient with a basal aneurysm being due to a coexisting pituitary adenoma must always be considered, and usually cannot be excluded during life unless a craniotomy is performed. The two lesions do in fact occur together (Cushing, 1912; Dandy, 1944), and three such cases, not described in this paper, have been observed at the National Hospital, Queen Square, in the past 15 years.

Summary

Three patients have been described with hypopituitarism associated with intracranial aneurysms. The possible ways in which endocrine abnormalities may be caused by an aneurysm are discussed, and it is suggested that there may be some interference with the vascular supply to the hypothalamus.

We should like to thank Dr. S. P. Meadows for his helpful criticism and encouragement, and for allowing us to use Cases 1 and 3, which were under his care in the Westminster Hospital. Mr. J. M. Small has very kindly given us particulars about Case 1 when she was in the Queen Elizabeth Hospital, Birmingham. We are grateful to Dr. John Marshall for permission to use Case 2, and to Dr. Q. J. G. Hobson for details of this case when under his care at the West Middlesex Hospital. We are indebted to Professor N. F. Maclagan and the Department of Chemical Pathology, Westminster Medical School, for the investigations in Cases 1 and 3. We should also like to thank Miss Jill Nuttall and the photographic department, Westminster Hospital, for the figures.

References

Appleby, J. I., Gibson, G., Norymberski, J. K., and Stubbs, R. D. (1955). *Biochem. J.*, **60**, 453.
Bauer, H. G. (1954). *J. clin. Endocr.*, **14**, 13.
Boothby, W. M., and Sandiford, I. (1929). *Amer. J. Physiol.*, **90**, 290.
Bozzoli, A. (1937). *Riv. oto-neuro-oftal.*, **14**, 304.
Bramwell, B. (1887). *Edinb. med. J.*, **32**, 911.
Brouwer, B. (1949). Personal communication, quoted by Meadows (1951).
Cushing, H. (1912). *The Pituitary Body and Its Disorders*, p. 97 (Case XV). Lippincott, Philadelphia and London.
Dandy, W. E. (1944). *Intracranial Arterial Aneurysms*, p. 33 (Case VI). Comstock Publishing Co., Ithaca, N.Y.
Dawson, B. H. (1958). *Brain*, **81**, 207.
Driesen, W. (1959). *Zbl. Neurochir.*, **19**, 28.
Du Bois, D., and Du Bois, E. F. (1916). *Arch. intern. Med.*, **17**, 863.
Escamilla, R. F., and Lisser, H. (1942). *J. clin. Endocr.*, **2**, 65.
Fraser, R., Hobson, Q. J. G., Arnott, D. G., and Emery, E. W. (1953). *Quart. J. Med.*, **22**, 99.
Gallagher, P. G., Dorsey, J. F., Stefanini, M., and Looney, J. M. (1956). *Neurology*, **6**, 829.
Girard, P. F., Guinet, P., Devic, M., and Mornex (1953). *Rev. neurol.*, **89**, 279.
Hamby, W. B. (1952). *Intracranial Aneurysms*, p. 147. Thomas, Springfield, Ill.
Hagedorn, H. C., and Jensen, B. N. (1923). *Biochem. Z.*, **135**, 46.
Höök, O., and Norlén, G. (1958). *Acta chir. scand.*, Suppl. 235.
Jefferson, A. (1957). *J. Neurol. Psychiat.*, **20**, 265.
Jefferson, G. (1937). *Brain*, **60**, 444.
Jenkins, D., Forsham, P. H., Laidlaw, J. C., Reddy, W. J., and Thorn, G. W. (1955). *Amer. J. Med.*, **18**, 3.
Lodge, S. D., Walker, G. F., and Stewart, M. J. (1927). *Brit. med. J.*, **2**, 1179.
Loraine, J. A., and Brown, J. B. (1959). *J. Endocr.*, **18**, 77.
Luft, R. (1958). In Discussion of Höök and Norlén (1958).
McDonald, C. A., and Korb, M. (1939). *Arch. Neurol. Psychiat. (Chicago)*, **42**, 298.

Marks, V. (1959). *Clin. chim. Acta*, **4**, 395.
Meadows, S. P. (1951). In *Modern Trends in Neurology*, p. 444. Butterworth, London.
Mecklin, B. (1950). *N.Y. St. J. Med.*, **50**, 1272.
Norymberski, J. K., Stubbs, R. D., and West, H. F. (1953). *Lancet*, **1**, 1276.
Offret, G., and Aron, J. J. (1959). *Bull. Soc. Ophtal. Fr.*, No. 3, 228.
Rhonheimer, C. (1959). *Klin. Mbl. Augenheilk.*, **134**, 1.
Schiefer, W., and Marguth, F. (1956). *Acta neurochir.*, **4**, 344.
Sheehan, H. L., and Summers, V. K. (1949). *Quart. J. Med.*, **18**, 319.
Sjöqvist, O. (1936). *Nervenarzt*, **9**, 233.
Staveren, P. J. van, and Smits, M. W. (1959). *Ned. T. Geneesk.*, **103**, 1525.
Weinberger, L. M., Adler, F. H., and Grant, F. C. (1940). *Arch. Ophthal. (Chicago)*, **24**, 1197.
Werner, S. C., Blakemore, A. H., and King, B. G. (1941). *J. Amer. med. Ass.*, **116**, 578.
White, J. C., and Ballantine, H. T. (1961). *J. Neurosurg.*, **18**, 34.
Zollinger, R., and Cutler, E. C. (1933). *Arch. Neurol. Psychiat. (Chicago)*, **30**, 607.

Preliminary Communications

Production of Calciphylactic Facial, Oesophageal, and Mediastinal Lesions by Combined Treatment with Dihydrotachysterol and Thorium Dioxide

Calciphylaxis is a condition of hypersensitivity in which, during a "critical period" after sensitization by a systemic calcifying factor (for example, vitamin-D compounds, parathyroid hormone), treatment with certain challengers (for example, metallic salts) causes an acute local tissue-calcification followed by inflammation and sclerosis. The topical calciphylaxis thus induced by subcutaneous injection of challengers results in a cutaneous calcinosis reminiscent of calcareous scleroderma. However, in suitably sensitized (for example, dihydrotachysterol-treated) rats, calciphylactic reactions can also be elicited rather selectively at predetermined sites (for example, in the pancreas, thyroids, parathyroids, bile ducts, uterus, spleen, Kupffer cells, lungs, salivary glands, lacrimal glands) by the intravenous administration of challengers that have a particular affinity for any one organ (Selye, Cantin, and Jean, 1960; Selye, Jean, and Veilleux, 1960; Selye, Grasso, and Dieudonné, 1961).

Here we should like to report on a curious calciphylactic syndrome that can be elicited by a single intravenous injection of thorium dioxide in suitably sensitized rats.

Materials and Techniques

Forty female Holtzman rats, with a mean initial body weight of 97 g. (range, 95–102 g.), were subdivided into four equal groups and treated as follows:

Group 1, dihydrotachysterol (D.H.T., or "calcamin" ®, Wander Co.), 1 mg. in 0.5 ml. corn oil, by stomach-tube on first day. *Group 2*, "thorotrast" ® (Testagar Co., a suspension containing 25 mg. of ThO_2/ml.), 1 ml., intravenously on second day. *Group 3*, D.H.T. (as Group 1) + thorotrast® (as Group 2). *Group 4*, D.H.T. (as Group 1) + thorotrast®, 0.6 ml., intravenously on second day.

The experiment was terminated on the sixth day by killing all survivors with chloroform. Specimens of various tissues were fixed in alcohol-formol (8 parts absolute alcohol, 2 parts 10% formaldehyde) for the subsequent histochemical demonstration of calcium phosphate by von Kóssa's silver-nitrate technique.

Results

The rats treated with D.H.T. alone or thorotrast® alone showed no noteworthy changes and therefore need not be discussed in detail here. Suffice it to point out that the single dose of 1 mg. of D.H.T. produced little or no metastatic calcification even in the organs (cardiovascular system, gastric mucosa, kidney) that are normally predisposed to the development of calcific

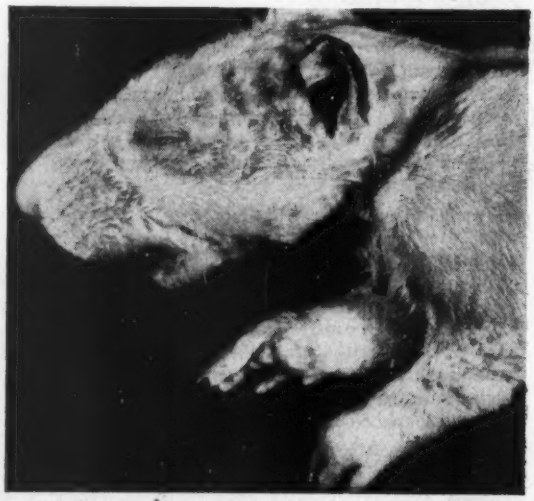


FIG. 1.—Typical aspect of the facial lesions induced by D.H.T. + thorotrast®. The fur was clipped and the left external ear removed in order to expose the swollen and calcified areas round the snout (which made it impossible for the animal to close its mouth) the eyelid, and the base of the external ear. In this instance the skin of the forepaws is also calcified, but this was rather unusual.

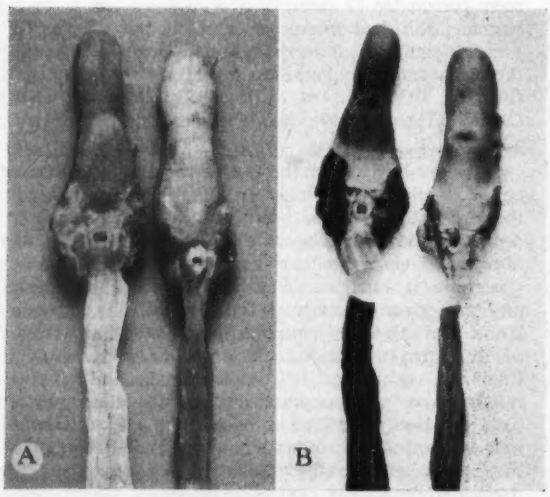


FIG. 2.—Macroscopic appearance of the pharyngeal and oesophageal lesions induced by D.H.T. + thorotrast®. A: Fresh specimens. B: After defatting and staining with $AgNO_3$. The organs on the left of each picture are those of the rat treated with D.H.T. + thorotrast®; the other specimens come from a control rat given D.H.T. alone.

deposits under the influence of heavy overdosage with vitamin-D compounds. Conversely, all rats treated with D.H.T. plus 1 or 0.6 ml. of thorotrast® (Groups 3 and 4, respectively), though apparently quite normal during the first two days, began to become manifestly ill on the third day. They developed a peculiar stiffness, swelling, and whitish discoloration of the skin of the snout, the eyelids and their surroundings, as well as round the base of the ears. These lesions progressed rapidly during the following days, and towards the end of the experiment the rats could no longer close their mouths because of the stiffening of the lips. In addition, the rats of these two groups developed a gasping type of breathing and had obvious difficulties in their attempts to swallow the occasional crumbs of food that they were able to ingest despite the stiffness of their lips (Fig. 1).

The reason for these difficulties in respiration and deglutition became immediately obvious at necropsy. Though the degree of the lesions was subject to slight individual variation, every animal in Groups 3 and 4 showed intense calcification in the musculature surrounding the fauces (soft palate, palatine arches, and base of the tongue), as well as in the oesophagus between pharynx and cardia (Fig. 2). Histologically, the calcium deposition at the root of the tongue was predominantly in the connective tissue and striated musculature, while in the oesophagus it occupied the entire thickness of the wall between the epithelium and the surrounding fascial layer (Fig. 3). In addition, particularly heavy masses of precipitated calcium salts were visible in the loose connective tissue surrounding the pulmonary hilus.

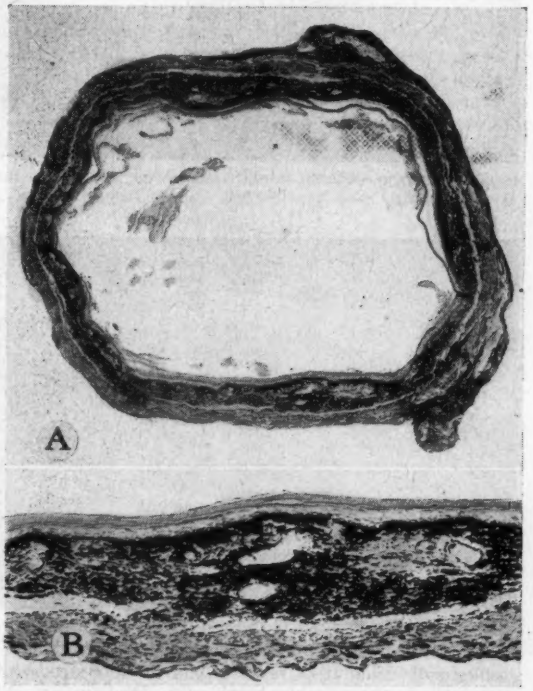


FIG. 3.—Histological appearance of the oesophagus after treatment with D.H.T.+thorotrast® A: Cross-section through the wall of the oesophagus shows continuous layer of calcium deposition in the wall (von Kóssa. ×35); B: Higher magnification of the oesophagus (corresponding to adjacent portion of picture above). Note strict limitation of calcification to connective tissue beween epithelium and outer facial layer (von Kóssa. ×120.)

There was surprisingly little calcification in any of the other organs, although occasionally some calcium incrustration occurred in the pulmonary septa and the spleen. Although heavy deposits of thorium dioxide were microscopically visible in the Kupffer cells and splenic phagocytes, calcium deposition never occurred in the liver and only occasionally in the periphery of the splenic Malpighian follicles. The cutaneous, pharyngeal, oesophageal, and mediastinal lesions all stained black with von Kóssa's procedure. The mineral deposits were associated with active connective-tissue proliferation and inflammatory infiltration, particularly by eosinophils and pseudo-eosinophils, the presence of which is especially characteristic of calciphylactic responses in general.

These lesions were accompanied by an intense acute osteitis fibrosa characterized by pronounced bone absorption with an abundance of osteoclasts, and fibrosis in the bone-marrow. The bones of the rats treated with D.H.T. alone showed no comparable lesions. It may be assumed that here—as in many other forms of calciphylaxis elicited by different challengers—the bone lesions result from an acute transposition of calcium from the skeleton into the affected soft tissues.

DISCUSSION

It would be premature to speculate upon the factors responsible for the singular distribution of the calciphylactic lesions that result when thorium dioxide is used as a challenger in the D.H.T.-sensitized rat. The cutaneous calcinosis induced by topical application of challengers (for example, metallic salts, mechanical trauma) to the skin of rats sensitized either by D.H.T. or by parathyroid hormone resembles the calcareous form of scleroderma (the so-called "sclérodermie calcaire" of French dermatologists). This similarity was pointed out long ago (Selye, 1932; Selye, Cantin, and Jean, 1960; Selye, Jean, and Veilleux, 1960). Now we learn that symmetrically arranged cutaneous lesions of this type can be induced in the skin of the face—even without any topical damage—by the intravenous injection of a thorium-dioxide preparation following sensitization by orally administered D.H.T. These experimental skin lesions are associated with similar connective-tissue responses in the oesophagus and mediastinum. This fact could also be taken to suggest the possibility of a connexion with systemic scleroderma, since the latter is known to exhibit a predilection for these same sites and there are few, if any, other systemic pathogens in either experimental or clinical pathology that exhibit a rather selective affinity for the skin, the oesophagus, and the mediastinal connective-tissue. Yet our data are far from proving the existence of any fundamental pathogenic relationship between the experimental syndrome that we produced and the spontaneous disease of man that it superficially resembles.

SUMMARY

Rats were sensitized by a single oral dose of dihydrotachysterol and, 24 hours later, challenged by a single intravenous injection of a thorium-dioxide suspension ("thorotrast"®). This treatment induced multiple morbid foci characterized by calcification, connective-tissue proliferation, and infiltration with inflammatory cells, among which eosinophils and pseudo-eosinophils predominate. The lesions tended to be selectively

localized in the facial skin, soft palate, palatine arches, base of the tongue, oesophagus, and mediastinal connective-tissue. The cutaneous changes thus produced resemble the calcareous form of scleroderma. It is emphasized, however, that neither this resemblance nor the singular localization of the associated lesions in internal organs proves any fundamental relationship between the pathogenic mechanisms responsible for the development of these experimental lesions and systemic scleroderma as it occurs in man.

This investigation was supported by the Medical Research Council of Canada (Consol. Gr. No. 11), by the U.S. Army Medical Research and Development Command, Contr. No. DA-49-193-MD-2039, and by the Department of Health and Welfare of the Province of Quebec.

HANS SELYE, M.D., D.Sc., F.R.S.C.
GIOVANNI GENTILE,* M.D.
RENÉ VEILLEUX,† D.V.
Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal, Montreal, Canada.

REFERENCES

Selye, H. (1932). *J. Amer. med. Ass.*, **99**, 108.
—— Cantin, M., and Jean, P. (1960). *Arch. klin. exp. Derm.*, **212**, 1.
—— Grasso, S., and Dieudonné, J. (1961). *Rev. Allergy and appl. Immun.*, **15**, 461.
—— Jean, P., and Veilleux, R. (1960). *Proc. Soc. exp. Biol. (N.Y.)*, **104**, 409.

Medical Memoranda

A Case of Extensive Interstitial Calcinosis

As cases of widespread calcinosis affecting skin and subcutaneous tissues are rare the following case is worth reporting.

CASE REPORT

The patient, a man aged 38, was first admitted to hospital in June, 1957. In January, 1956, he developed pyrexia—103–103.5° F. (39.4–39.6° C.)—and painful swelling of the joints of the hands, wrists, ankles, elbows, and knees. These persisted for one month and then gradually subsided, but some stiffness of the hands and some painful limitation of movements of the elbows and knees still persisted. One year later he again developed pyrexia—103–103.5° F. (39.4–39.6° C.)—and painful swelling of the same joints persisted for five months until admission, while for the last 40 days his general condition greatly deteriorated, and an erythematous rash appeared on his face. Ten days before admission steroid treatment was started.

On admission his temperature was 103.5° F. (39.6° C.). He was an ill-looking, wasted man with diffuse slightly desquamating erythema on the face. There were marked painful swelling and limitation of movements of all metacarpo-phalangeal and proximal interphalangeal joints, wrists, elbows, ankles, and knees. His hands were bluish and cold, with some atrophy of the interossei muscles.

On investigation the haemoglobin was 11.2 g./100 ml.; W.B.C., 5,200 (normal differential); E.S.R. 110 mm./1st hour (Westergren). No L.E. cells were found after numerous examinations. Serum proteins, electrolytes, urea, sugar, liver-function tests, and E.C.G. were normal. Urine showed scanty erythrocytes. *X*-ray pictures of chest, hands, skull, pelvis, and thighs were normal.

The high pyrexia, the joint involvement, and the rash rendered the diagnosis of disseminated lupus erythematosus (D.L.E.) highly tenable. The absence of L.E. cells could perhaps be attributed to the steroid treatment prior to admission. After intensive steroid treatment in hospital his general state improved considerably; the pyrexia subsided completely, and the joint changes greatly improved. He was discharged in September, 1957.

Second Admission.—He was readmitted in January, 1959. He had been relatively well since his discharge, receiving a maintenance dose of 20 mg. of prednisolone daily. For the three months prior to this admission he had felt weak and tired. On examination his general condition was fairly good, diffuse erythema over the whole face; moderate swelling and limitation of movement of the fore-mentioned joints. His hands were bluish and cold. On palpation the skin, subcutaneous tissue, and muscles were of normal structure, but large calcium deposits were felt about the elbows and knees. Radiographs showed calcifications of the soft tissues at these areas. He was discharged in March, 1959.

FIG. 1.—Calcium deposits in the wall of the pelvis and the abdomen.

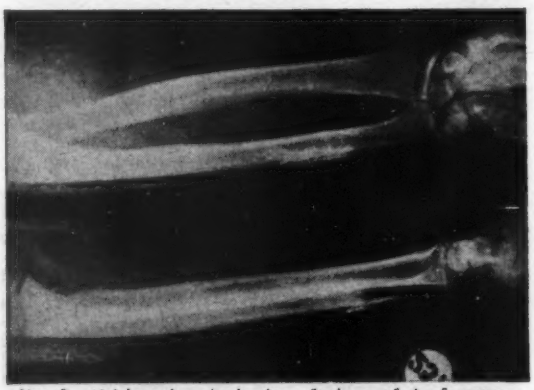


FIG. 2.—Calcium deposits in the soft tissue of the forearm.

Third Admission (August, 1960).—He had felt moderately well on a maintenance dose of 15 mg. of prednisolone daily. Five days before admission he had a mild pyrexia—100.5–101.5° F. (38–38.6° C.)—and a painful redness at the lower third of the right arm. On examination he was a fairly healthy-looking man; temperature 100.2° F. (37.9° C.). Diffuse erythema was present over the whole face. His hands were bluish red, and there were marked atrophy of the interossei muscles. Massive calcium deposits were present on the arms, the upper third of the forearms, the buttocks, the posterior and lateral aspects of the thighs, the

*Fellow of the Gustavus and Louise Pfeiffer Research Foundation.
†Fellow of the National Research Council of Canada.

upper third of the legs, and the lower part of the abdomen. Around the calcium deposit over the right elbow there was inflammation with a discharging ulcerated area.

Investigations now gave the following results: Urine: albumin ++, scanty erythrocytes, numerous casts. Hb, 16.1 g./100 ml.; W.B.C., 6,000 (normal differential); E.S.R. 57 mm./1st hour (Westergren); L.E. cells absent; R.A. test and latex test negative; routine biochemical blood tests normal. Liver-function tests: thymol turbidity 8 units; cephalin cholesterol +++; $ZnSO_4$ turbidity, 18 units. Serum electrophoresis: decrease of albumin, increase of α_2- and γ-globulin. Blood calcium, 11.8 mg./100 ml. (normal value 9–12 mg./100 ml.). Urine calcium 200 mg./24 hours. *X*-ray pictures of chest, oesophagus, stomach, colon, and spine were normal. Radiographs of limbs and pelvis showed widespread calcifications of the soft tissue of the pelvis, abdominal wall, thighs, arms, and forearms (Figs. 1 and 2). Biopsy revealed marked calcium deposits in the subcutaneous tissue and muscle.

Comment

This case presents the typical picture of extensive interstitial calcinosis. Wheeler *et al.* (1952) have reviewed 66 cases of calcinosis, both circumscripta and universalis, of which 54 were collected from the literature and 12 were from their own material. Dermatomyositis was the primary disease in 24 cases, scleroderma in 24, and D.L.E. in only one. In the present case the clinical picture initially resembled that of D.L.E., but in later stages that of dermatomyositis or scleroderma; yet biopsy failed to show the changes of either condition.

C. Gardikas, M.D., M.Sc., Ph.D.,
J. Hadjioannou, M.D.,
Second Medical Unit, Evangelismos Hospital, Athens.

Reference

Wheeler, C. E., Curtis, A. C., Cawley, E. P., Grekin, R. H., and Zheutlin, B. (1952). *Ann. intern. Med.*, **36**, 1050.

Self-induced Fatal Air Embolism in a Man

Self-induced fatal air embolism is probably not very rare, mainly occurring in women who douche to get rid of unwanted pregnancies. Cooke (1950) reported the case of a woman who had a cervical erosion and happened to be pregnant. Simpson (1958) made the important point that death may not be immediate or even rapid, when he described the case of a woman of 35 who collapsed and died several hours after the instrumentation.

In the male, however, the condition is very rare, which is perhaps surprising in view of the bizarre acts practised by some in the hope of relieving sexual tensions. For example, Fox and Barrett (1960) reported three cases of vacuum-cleaner injury to the penis, only slight local damage resulting.

In the following case fatal air embolism is believed to have resulted from self-insufflation of the urethra with a Higginson syringe. As a coincidence the thyroid gland showed the widespread histological picture of lymphadenoid thyroiditis of Hashimoto type, a condition itself rare in males.

Case Report

A man of 69, living alone, was found dead on his hearth-rug beside an overturned chair. He was fully clothed, including a cloth cap and spectacles, but his trousers were down round his feet and his shirt was neatly rolled up to his chest. A broken pudding-bowl was 2 ft. (30 cm.) away, but it was dry. His right arm was extended on the floor and the left was across his chest and a Higginson syringe was in this hand, both ends being loose and free; only a small amount of spray emerged when the bulb was squeezed.

Necropsy was carried out about 12 hours after death, the findings being as follows. Body of good average nourishment and rigor mortis fully established; large right scrotal hernia; a short superficial split of the skin on the back of the right forearm, and some vomit stain round the mouth. Small bilateral pleural effusions and lungs congested and the left also oedematous. The right ventricle of the heart was rounded and contained frankly frothed blood, and this was also present in the main pulmonary arteries. The urinary bladder appeared slightly rounded, but was empty of urine; no evidence of injury in the lining of the anal canal or rectum was seen, but the urethral lining showed numerous vivid petechiae; these were present in a group just inside the meatus, beyond which the mucosa was almost clear for 4 cm., and then the petechiae were numerous again over the 10 cm. back to the prostate, which was of normal size and appearance; the bladder mucosa was also normal, and showed no trace of haemorrhage. The thyroid gland was somewhat enlarged and abnormally firm. There was frank atheromatous thickening almost throughout the main coronary branches, yet their channels were wide, and the heart muscle and valves were normal. The cause of death was given as "air-embolism due to haemorrhages in the urethral mucosa as a result of distension with air."

Histology.—The thyroid gland showed the coarse lobulation, dense widespread infiltration with lymphocytes and plasma cells (including numerous lymphoid follicles with germ centres), and compression and disorganization of the gland acini throughout, with widespread "pseudo-giant-cell" formation, all typical of Hashimoto thyroiditis. The liver was normal. The kidneys showed fibrosis of a few glomeruli only.

I thank Mr. Norman Graham, H.M. Coroner, Stockton Ward, Co. Durham, for permission to describe this case; and Dr. James Davson, of Manchester, for his confirmation of the thyroid-gland histology.

R. T. Cooke, M.D.,
Department of Pathology,
General Hospital, West Hartlepool.

References

Cooke, R. T. (1950). *Brit. med. J.*, **1**, 1241.
Fox, M., and Barrett, E. L. (1960). *Ibid.*, **1**, 1942.
Simpson, K. (1958). *Med.-leg. J. (Camb.)*, **26**, 132.

"But every now and again someone makes a discovery which significantly extends the horizons of knowledge. The immediate effect of a significant discovery is disruptive. Contrary to common belief, it doesn't always enable you to use your present equipment of knowledge more fully; it is more likely to render your present equipment of knowledge out of date. It may make whole professions or industries superfluous. It may create unemployment not only among operatives, but also among general managers and chief chemists and engineers. . . . No wonder a great discovery—once its consequences are realized—is received with anxiety and dread. No wonder it is resented by the very professionals and experts whose own skills are made obsolete by it. Established knowledge, codified knowledge, examinees' knowledge, may well become the greatest obstacles to the acceptance of a significant discovery. Erudition and competence may be the most sinister enemies of research and invention. This is the paradox. The training you have had here is the foundation of your skill in your profession. You cannot be expected to welcome any discovery which undermines that foundation. Yet obsolescence is built into that training, as surely as it is into the lines of a flashy new car." (Sir Eric Ashby (Master of Clare College, Cambridge), inaugural address, 120th session, School of Pharmacy, London.)

Reviews

THE FIFTEENTH "MANSON'S"

Manson's Tropical Diseases. A Manual of the Diseases of Warm Climates. Edited by Sir Philip H. Manson-Bahr, C.M.G., D.S.O., M.A., M.D., D.T.M.&H.Cantab., F.R.C.P. Lond., M.D.(Malaya, Hon. Causa). Fifteenth edition. (Pp. 1,177+xiv; illustrated. 84s.) London: Cassell. 1960.

Continuing as a memorial to its originator, the father of tropical medicine, and edited for the last 40 years by a worthy disciple in the same field, *Manson's Tropical Diseases*, which first emerged in 1898, reappears in its fifteenth edition. A standard work on its subject and without parallel, the present edition continues, as did its immediate predecessors, to be the very remarkable accomplishment of a single person. The labour devoted to its production is evident in the substantial revisions demanded by the considerable advances in knowledge since the previous edition of six years ago. The volume can be described as encyclopaedic: every aspect—epidemiological, clinical, pathological, and therapeutic—of nearly every condition thought of as tropical is authoritatively dealt with. In addition there is a comprehensive account of those parasites, both protozoal and helminthic, which may infect man and of the vectors responsible for their transmission or maintenance and the means for their control. The amount of accurate information it contains is prodigious.

When any question arises within the field of tropical medicine it has for long been good advice to "look it up in Manson-Bahr." That advice is still as sound to-day both for teacher and for student. For the practitioner who practises in the Tropics this work is an indispensable part of his basic equipment.

A. R. D. ADAMS.

SHOULDER DISLOCATION

Recurrent Dislocation of the Shoulder. By H. F. Moseley, M.A., D.M., M.Ch.(Oxon.), F.R.C.S.(Eng. and Canada), F.A.C.S. (Pp. 163+xii: illustrated. £6.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

Although Horace wrote of the "mountains which in labour bring forth a ridiculous mouse," the inversion, quoted by the author from Merton College in answer to a possible captious critic, is not inappropriate even if incorrectly Horatian: "*Parturiunt mures, nascetur ridiculus mons.*" Far from being ridiculous, this massive work is a wholly admirable collation of many men's ideas and studies illuminated by the author's intense devotion to the problems of the shoulder-joint. There are some novel features, including comments from living authorities in the same field who have been invited to review to-day what they may have said years ago—a useful exercise, for so many quotations of opinions or observations are not only out of date but are treated by the authors who use them as being products of ignorant and inferior minds. We must always be humble in discussing previous error, for what is false in yesterday's truth may in the future equally be so of to-day's.

All this is recognized by Mr. Moseley, who gives a carefully balanced review of the past and present in the much-discussed "basic lesion" underlying recurrent dislocation—a theory which was so clearly presented by Bankhart and is here graciously recorded by Wiles. The work is beautifully illustrated. Anatomical backgrounds and operative steps are almost all portrayed in three ways: by coloured drawings, line drawings, and black-and-white half-tone. Furthermore (and this is the most novel feature) the book is provided with stereo diapositives in colour, placed in a pocket in the cover, complete with folding viewer. These pictures are of actual operative surgical sequences; while giving added information, they are somewhat disturbing because of the peculiar accentuation of depth produced photographically.

At the risk of seeming captious, I would suggest that the understanding of recurrent dislocation of the shoulder might have been aided by a fuller discussion of the anatomy of the whole shoulder girdle and its orientation with the thorax in different phases of movement. Nevertheless, one is lost in admiration of Mr. Moseley's monumental work, which should be in every orthopaedic surgeon's library. Livingstone's have excelled themselves in the book's production.

NORMAN CAPENER.

BETWEEN CONCEPTION AND BIRTH

Ciba Foundation Symposium on Congenital Malformations. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Cecilia M. O'Connor, B.Sc. (Pp. 308+xii; illustrated. 45s.) London: J. and A. Churchill, Ltd. 1960.

It is probable that the most critical period of our lives has always been between conception and birth, but increasing control of post-natal environment has rightly fixed attention on wastage due to congenital malformations, and these papers (and the discussions which follow) give a good idea of what we do and do not know about the subject in man and in animals.

McKeown and Record give us the baseline with the incidence, sex-ratio, and life expectancy of 57,000 births collected prospectively in Birmingham, and the data are particularly interesting when compared with other countries—malformations affecting the nervous system, mongolism, and talipes are much commoner and congenital dislocation of the hip much rarer here than in Japan.

Penrose, discussing genetic causes of abnormalities, points out that clear-cut syndromes such as polydactyly are rare and that what we meet more commonly is an inherited susceptibility—for example, to hare lip or cleft palate. Because environment can bring about somatic mutation and this in turn upset development it is increasingly difficult, as he points out, to distinguish between environmental and genetic factors. Both Penrose (and C. E. Ford in more detail) discuss the malformations brought about by known chromosomal abnormalities, the essential point being that either too much or too little chromatin can be damaging to the foetus.

To a clinician Ingalls seems on firm and fascinating ground. Rubella we know about, but maternal influenza and foetal hypoxia are probably also important and most interesting details are given of the distribution of congenital heart disease at different altitudes. Carbon monoxide poisoning has also produced malformations and a similar circumstance may possibly occur in severe asthmatics who are treated with morphine while pregnant.

From the practical point of view the paper by Hoet and his colleagues is of great importance. Maternal

pre-diabetes and hypothyroidism seem to be frequent causes of teratogenesis—the mechanism in both cases being probably *via* disturbance of carotene metabolism, since it is known that either hypo- or hypervitaminosis A can produce malformations in animals. In any case treatment of the mother is markedly effective for subsequent pregnancies.

The papers on animal experiments are patchy. On the one hand it is most informative to know that runts in mice can largely be accounted for by a poor blood supply *in utero* (McLaren and Michie) but on the other it seems unimaginative to kill large numbers of pregnant rats after injecting them with known antimetabolites which could scarcely do otherwise than produce foetal abnormalities—though folic acid antagonists seem to be so powerful that they might be used as abortifacients in man (M. Lois Murphy, Marjorie Nelson). An experiment of better design is that of Woollam and Miller, who find that in rodents the teratogenic activity of hypervitaminosis A (but not that of *X*-radiation) is markedly reduced by giving thyroxin, and the protective action of other drugs is also discussed.

Altogether this is a most interesting symposium and it can be strongly recommended, though the reviewer feels that foetal development is so species-specific that future progress lies more in studying man than the lower animals.

C. A. CLARKE.

NERVE BLOCKS

Clinical Applications of Diagnostic and Therapeutic Nerve Blocks. By John J. Bonica, M.D. (Pp. 354+xix; illustrated. 70s.) Oxford: Blackwell Scientific Publications. 1960.

In the preface the author claims that his monograph is not just a potted version of his well-known and encyclopaedic volume *The Management of Pain.* Nevertheless, some of the same ground is covered, but obviously with brevity, and with more emphasis on the approach of the physician to the patient suffering from pain than on the more technical exercises involved. The psychological approach described and the attitude that nerve blocks are only part of the treatment make welcome common-sense reading.

Without implying any unfavourable comparison, the appearance of this book, which is largely sponsored by the American Society of Anesthesiologists, so soon after a similar publication (*Fundamentals of Nerve Blocking* by Vincent J. Collins, 1960) may detract from its popularity. It does, however, emphasize how important our American colleagues consider this aspect of a physician's work.

The first 100 pages are devoted to basic considerations and the remainder of the book to specific problems and the techniques which may be employed in their relief. Comparatively little space is devoted to the mechanical details of placing a needle correctly, and reference to other textbooks is recommended for this purpose. This may at first sight seem a tedious diversion. On the other hand, it allows a clear discussion of the real subject matter of the book—the application of nerve blocks—which might otherwise be overwhelmed by minutiae. Quite properly, too, it is assumed that the practitioner should at least be technically competent before he is let loose on those brought near to breaking point by their suffering. This book succeeds in transmitting much of the author's sincerity and enthusiasm and will make many wish to see him at work. In spite of a number of illustrations in black-and-white the price seems somewhat high even for a book produced in the pleasing format now characteristic of the publishers.

R. BRYCE-SMITH.

SCIENTIFIC BASIS OF MEDICINE

The Scientific Basis of Medicine: Annual Reviews, 1961. By the British Postgraduate Medical Federation. (Pp. 342+vii; illustrated. 40s.) London: The Athlone Press, University of London. 1961.

London University is now publishing the talks previously known as *Lectures on the Scientific Basis of Medicine* under the title *The Scientific Basis of Medicine: Annual Reviews.* This more accurately describes the papers collected here, and though, as with wine, tastes and opinions may vary, it seems that 1961 will prove to be a vintage year. A wide range of topics has been chosen, and the authors are not only acknowledged experts but are still in the front line of the battle, contributing much from their own endeavours. The volume is well printed in attractive type on good paper, the illustrations are clear, and the line drawings reproduced in a uniform style. The cost is very reasonable.

The reviewer cannot do more than list some of the contents and authors, not giving all the titles because of limitations of space, and making this invidious selection only on the grounds that some of the papers have greater immediate appeal to the medical profession than others: "Genetic Analysis via Somatic Cells" (Pontecorvo); "The Antiviral Action of Interferon" (Isaacs); "Immune Cellular Reactions" (White); "The Relation of Radiation Dose to Skeletal Damage from Bone-Seeking Isotopes" (Vaughan); "Autoradiography in Bone Marrow Studies" (Lajtha); "Epidemiological Methods in Leukaemia Research" (Doll); "Fever and Pyrogens" (Pickering); "Blood Enzymes in Diagnosis" (Wilkinson); "Disorders of Aminoacid Metabolism" (Milne); "Non-pancreatic Aspects of Diabetes Mellitus" (Gray); "Liver Failure" (Sherlock); "Liver Regeneration" (Harkness); and "Magnesium Metabolism in Man" (Fourman).

R. I. S. BAYLISS.

INJURIES TREATED SURGICALLY

Surgical Treatment of Trauma. Edited by Preston A. Wade, M.D. (Pp 779+xii; illustrated. $26.50.) New York and London: Grune and Stratton. 1960.

It is significant that within the last twenty-four months three textbooks on the general subject of trauma have been published in the United States by the surgical staffs of large teaching hospitals. Increasing numbers of road accidents have introduced new surgical problems of some complexity with their greater severity and multiplicity of injuries. Practical instructions in the treatment of injuries to all parts of the body have therefore become a necessary part of the training of all surgeons who daily face these responsibilities. And as the foreword of this most recent American work states: "The matter of trauma as a medical problem has been given great consideration in recent years in both graduate and undergraduate training programmes."

In 1956 the Cornell University Medical College with the New York Hospital and the Hospital for Special Surgery presented the first of a series of annual post-graduate courses on the general subject of injuries. This book is a written review of the various lectures given on that and subsequent courses. It begins with a

consideration of such general principles as wound healing, the metabolic response to injury, traumatic shock, and the care of multiple injuries. Then follows a comprehensive chapter on general considerations in fracture treatment, with, not unexpectedly, the typical American trend towards open reduction. Yet it is good to read: "In spite of the fact that we use operative methods in our clinic in many cases, the great majority of fractures are treated by manipulation and immobilization in plaster splints. We do not consider operative treatment as 'radical' or closed methods of treatment as 'conservative.' It may be that the operative method may be more conservative than the closed method." I find no cause for disagreement with this statement, particularly in a victim of multiple injuries. Then follow chapters on injuries to the head, to the neck and spine, to the chest and abdomen, and, finally, special articles on a wide range of injuries to the extremities.

Thirty-five contributors, under the editorship of Dr. Preston A. Wade, have succeeded in presenting an excellent and clearly written review on a very comprehensive subject. If the book has a fault it stems from its multiplicity of authors, each a specialist in his subject. This leads inevitably to repetition, which is no bad thing, but it has also resulted in the exclusion of detail sometimes on matters of importance. For example, in the well-written article on "Fractures of the Pelvis and Complicating Injuries" and in the shorter article on "Injuries to the Urethra and Genitalia," the fact that a rupture of the posterior urethra can complicate a pelvic dislocation or a crushed pelvis is mentioned in both. Yet the important matter of reducing and holding the bony deformity in order to make close approximation of the soft tissue component of the wound possible is not described. This, in the land of open reductions, is a surprising omission. Yet it may indicate a need, and there is a need when many specialists treat one patient, for the closest co-ordination of effort. This co-ordination can only be achieved by "centring the full responsibility for the injured person on one surgeon, leaving it to him to secure such assistance as he may deem necessary."

Finally this reviewer cannot accept the implied contention on page 401 of a "seat belt syndrome" relating fractured pelves to the wearing of pelvic restraining harness. There is no evidence for this in American, Swedish, or British research on crashes where car occupants were wearing safety belts. Fractured pelves and complicating injuries are much more frequently seen as a result of road accidents to pedestrians and motor-cyclists than to car occupants.

WILLIAM GISSANE.

AT THE BEDSIDE OF GENIUS

13 Famous Patients. By Noah D. Fabricant, M.D. (Pp. 231 +ix; illustrated. 30s.) Philadelphia, New York: Chilton Company. 1960.

The diseases of four politicians (F. D. Roosevelt, Hitler, Gandhi, and Woodrow Wilson), six writers (Marcel Proust, D. H. Lawrence, James Joyce, Scott Fitzgerald, Freud, and Clarence Darrow—it is hard to understand why Freud and Darrow are grouped with the writers), and three artists (Gauguin, George Gershwin, and Enrico Caruso—strange bedfellows, but illness and death are great levellers) are related in this book with additional biographical details.

There are many reasons, not all of them flattering to mankind, why the diseases of genius and the illnesses of the great have a constant attraction for the reading public. To be admitted to the private life of public figures is a diminution of their stature and an elevation of ours; reverence is then diluted with pity, and admiration may be abated by fellow feeling. To recognize that their distinguished flesh is both weak and mortal may subtract from the discomfort which the inferior can experience in the presence of superior persons. We may justifiably reflect, too, that a price has to be paid for eminence and achievement.

There are, however, many pitfalls for physicians who would essay the diagnosis of the departed great. Those who have experienced the difficulty of total diagnosis in the living—all the playable cards on the table and all the reports back from the laboratory—are not likely to view without scepticism the retrospective medical protocols derived from the source books of history. Did Henry VIII have syphilis, Napoleon Bonaparte epilepsy, and was Elizabeth I no virgin? The evidence is so incomplete that a modern jury might well bring in a verdict of not proven. Few historical figures have documented their illnesses so well for posterity as did Samuel Johnson, Samuel Taylor Coleridge, and Charles Darwin.

Dr. Fabricant has not altogether avoided these difficulties by choosing his patients from the recent past. The course of Woodrow Wilson's illness is clear enough, but the cause of Roosevelt's decay remains a matter of medical opinion, and the psychopathology of Adolf Hitler depends on a personal interpretation of his public behaviour. Dr. Fabricant does not attempt any analysis of the illness and personality of Proust, Lawrence, Gauguin, and Joyce, nor does he seek to relate their pathology to their achievement, and perhaps for this we should be grateful. For in truth we cannot have complete confidence in him as a historian, since he inclines to indulge too easily in the cosmic conjecture. On the first page he writes, "Had the fates decreed that a young wife and her infant son (F.D.R.) should die during childbirth on the evening of January 30, 1882, because of an overdose of chloroform, the course of American history would have been irretrievably altered." And on the last page of his book he gives us a final forecast, "Had Enrico Caruso lived to the present era, antibiotics and sulphonamides would have cured his original infection, and his golden voice would then have continued to thrill listeners for years to come."

Nor are Dr. Fabricant's medical opinions likely to win universal assent, as, for example, when he writes, "Chloroform fumes are irritating to respiratory mucous membranes. It is therefore not surprising, in light of the overdosage to which mother and infant had been subjected, that the common cold, by far the most democratic of all the ills that were to plague young Franklin the rest of his life, occurred when he was several days old."

A book for the low-brow library list.

D. V. HUBBLE.

BACTERIOLOGY FOR NURSES

Bacteriology and Immunity for Nurses. By Ronald Hare, M.D. (Pp. 193+viii; illustrated. 17s.) London: Longmans. 1961.

An advance in any field of medicine may alter nursing practices. Some form of specific therapy is now available for almost every bacterial infection. Where possible laboratory assistance is desirable in establishing the diagnosis and in suggesting the most suitable drug

for treatment. In all this nurses are inevitably concerned. They usually, for instance, collect the specimens for laboratory examination, and unless the specimen is collected properly the bacteriologist's report may only mislead. They, too, are concerned with treatment, and particularly with the problems of cross-infection which have accompanied the expanding use of antibiotics. In time it will be possible to prevent hospital infection by measures based on an understanding of the way in which bacteria spread. This time has not yet come, and nursing practices are compounded from a mixture of sound epidemiological knowledge, untested hypotheses, and traditional lore, with the frequent addition of supplementary precautions to satisfy the current views of a member of the staff.

To the nurse who is prepared to read beyond the strict limits of the examination syllabus Professor Hare's new book should be very welcome. In it she will find a readable account of bacteria and viruses in general, and notes on individual organisms which cause human disease. Immunity, immunization, diagnosis, and treatment all receive attention. Prevention of infection, a subject on which the author speaks with special knowledge, is given pride of place. As an outline for nurses of present views on bacteriology and immunity it is excellent. The publishers are to be congratulated on producing it for 17s.

R. A. SHOOTER.

RUSSIAN RESEARCH

Evolutionary Regularities as Reflected in the Epileptiform Reaction of Animals to High Partial Oxygen Pressure. By A. V. Voino-Yasenetskii. (Pp. 136; illustrated. No price.) Moscow, Leningrad: The Academy of Sciences of the U.S.S.R. 1958.

This monograph has been translated and published by the National Science Foundation, Washington, which is doing much valuable work of this sort to bring Russian science to our notice. It contains the protocols of experiments, particularly those performed on small reptiles, the behaviour of which has been studied under varying partial pressures of oxygen. These results are related to Orbelis's observations upon the evolutionary meaning of physiological differences in species. The text is highly specialized, but it gives access to a wide Russian literature.

DENIS WILLIAMS.

DERMATOLOGY FOR STUDENTS

Dermatology for Students. Edited by Ray O. Noojin, M.D. (Pp. 301+xiii; illustrated. 76s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

The editor chose about twenty-five common skin diseases and asked a similar number of dermatologists to contribute a chapter on each. The result is unsatisfactory and does justice neither to the subjects chosen nor to the contributors. The work is uneven in quality and lacks coherent presentation, and is a particularly unsuitable way to introduce any branch of medicine to the student. Many of the contributions are inadequate for the purpose intended; a few—such as those on acne, dermatitis venenata, and herpes—are good.

The illustrations in black-and-white are generally poor by modern standards and this is true of many of the coloured plates. The work as a whole is not to be recommended.

J. T. INGRAM.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Obstetrical Emergencies. By Denis Cavanagh, M.B., Ch.B. (Glasgow), F.A.C.O.G. (Pp. 380+xxii; illustrated. £5.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

The Electroencephalogram of the Normal Child. By Alberto Fois, M.D. Translated and edited by Niels L. Low, M.D., F.A.A.P. (Pp. 124+xvi; illustrated. 54s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

The Exercise Electrocardiogram in Office Practice. By E. Grey Dimond, M.D., F.A.C.P. (Pp. 169+ix; illustrated. 80s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961.

Proceedings of the 1st European Symposium on Medical Enzymology, Milan, 1960. Editor: Nicola Dioguardi. (Pp. 575; illustrated. Sw. Fr. 70.) New York, Basle: S. Karger. 1961.

Präparation des Gehirns. By Gabor Inke, with the collaboration of B. Zolnai. (Pp. 92; illustrated. DM. 18.80.) Jena: Veb Gustav Fischer Verlag. 1961.

International Review of Cytology. Edited by G. H. Bourne and J. F. Danielli. Volume II. (Pp. 356+xii; illustrated. 88s.) New York, London: Academic Press. 1961.

Your Book of the Human Body. By John Burkinshaw, M.R.C.P. (Pp. 100; illustrated. 10s. 6d.) London: Faber and Faber. 1961.

Les Cancers du Massif Maxillaire Supérieur. Étude Anatomo-Clinique et Thérapeutique. By P.-C. Huet and S. Stefani. (Pp. 259; illustrated. NF. 50.) Paris: Masson et Cie. 1960.

The Use of Drawing in the Study of Anatomy and Physiology. By Charles R. Bannister, M.C.S.P. (Pp. 39; illustrated. 17s. 6d.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

An Introduction to Clinical Electro-Encephalography. By Robert R. Hughes, M.D., M.R.C.P. (Pp. 118+vi; illustrated. 30s.) Bristol: John Wright and Sons Ltd. 1961.

Le Occlusioni Intestinali Congenite. By Antonio Righini. (Pp. 155; illustrated. No price.) Pisa: Edizioni "Omnia Medica." 1961.

An Introduction to Anaesthetics. By John D. Laycock, M.B., B.S., F.F.A.R.C.S. (Pp. 132. 10s.) London: Lloyd-Luke (Medical Books) Ltd. 1961.

Therapeutic Exercise. Second edition. Edited by Sidney Licht, M.D., assisted by Ernest W. Johnson, M.D. (Pp. 959+xvi; illustrated. $16.) New Haven, Conn.: Elizabeth Licht. 1961.

Physiology of the Digestive Tract. By Horace W. Davenport, Ph.D., D.Sc. (Pp. 221; illustrated. 64s.) Chicago: Year Book Medical Publishers Inc. 1961.

Manual of Pediatric Physical Diagnosis. Second edition. By Lewis A. Barness, M.D. (Pp. 208; illustrated. 30s.) Chicago: Year Book Medical Publishers Inc. 1961.

Fundamentals of Acid-Base Regulation. By James R. Robinson, M.D., Ph.D. (Pp. 78+x. 9s. 6d.) Oxford: Blackwell Scientific Publications. 1961.

Chemotherapy of Tuberculosis. By William F. Russell, jun., M.D., M.S., and Gardner Middlebrook, M.D. (Pp. 130+xi; illustrated. 52s.) Springfield, Illinois: Charles C. Thomas. 1961.

The Black Death: A Chronicle of the Plague Compiled from Contemporary Sources. Translated by C. H. Clarke, Ph.D. (Pp. 159; illustrated. 6s.) London: Unwin Books. 1961.

Vertebral and Carotid Angiograms in Tentorial Herniations. By Hans F. Plaut, M.D. (Pp. 155; illustrated. 84s.) Springfield, Illinois: Charles C. Thomas. 1961.

Clinical Audiometry. By Michael Portmann, M.D., and Claudine Portmann, M.D. (Pp. 349+xxvi; illustrated. 96s.) Springfield, Illinois: Charles C. Thomas. 1961.

An Introduction to Functional Anatomy. By David Sinclair, M.A., M.D. (Pp. 447; illustrated. 42s.) Oxford: Blackwell Scientific Publications. 1961.

Studies in Quantitative Organic Micro-analysis. By Wolfgang Johannes Kirsten. (Pp. 19. No price.) Uppsala: Wretmans Boktryckeri AB. 1961.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY NOVEMBER 4 1961

MANAGEMENT OF ATTEMPTED SUICIDE

Now that attempted suicide is no longer a criminal offence[1] the Ministry of Health[2] has sent a timely memorandum to general practitioners, local authorities, and hospitals advising on the management of these cases. The memorandum emphasizes that attempted suicide is now to be regarded entirely as a medical and social problem; that cases going to hospital to receive first aid are not consistently given the psychiatric help they require; and that social support and follow-up care will now more than ever be needed from the psychiatric services, the general practitioner, and the local authority.

It is difficult to obtain a reliable figure for the annual number of attempted suicides, though the rate based on the cases known to the police in 1951 was about 14 per 100,000 population in London.[3] The Suicide Prevention Center in Los Angeles undertook a survey to determine the number of serious attempts made in the city during 1957.[4] Their estimated figure was 6,000 to 7,000 cases, giving a rate for attempted suicide at least eight times the rate for successful suicide. Were the same ratio to obtain in England and Wales there would be some 40,000 cases a year. Clearly the problem is fairly large.

In order to devise a sound policy for the treatment and aftercare of attempted suicides information of three kinds is needed: the extent to which people who attempt suicide later succeed or make further attempts; the characteristics by which cases with a high risk may be recognized; and lastly the extent to which attempted suicide is associated with medical or psychiatric disorders and environmental conditions for which there are effective remedies.

Follow-up studies of patients admitted to hospital after attempted suicide show that only a small proportion eventually commit suicide—probably less than 1% per year of follow-up, though there are indications that the rate is higher in those referred to a general hospital than those who are admitted to psychiatric units. Further suicide attempts are made more frequently. Stengel reported 17% of those he followed up for four years made another attempt and often more than one[3]; a study in St. Louis gave a somewhat lower figure.[5]

Recent work on attempted and successful suicide broadly indicates the characteristics by which the case with a high risk of suicide may be recognized.[3–8] Perhaps of first importance is the patient's own attitude to his attempt. Nearly all patients when questioned will admit in so many words whether they intended to die, how seriously they meant to, and whether they still want to. When the suicide intent is high the attempt is more often deliberately planned, whereas the suicidal gesture is usually either of a more impulsive character or openly advertised in advance. About 70% of successful suicides give a covert warning to their family or their doctor of their distress which should be sufficient to put them on their guard.[9 10] The method of suicide may also help to distinguish the more serious attempt, as may the conspicuousness with which the preparations for it were made.

The symptoms and signs of depression which may still be present after the attempt are important clues. A depressive illness is the condition most strikingly associated with successful suicide and with seriousness of intent, though it has recently been indicated that depression and suicide are not synonymous.[7] It has been calculated that 14% of patients with psychotic depressions will eventually commit suicide.[8] The risk is especially high among elderly depressives.[11] The little we already know about the clinical recognition of the depressive who is a potential suicide is still insufficiently widely taught. For example, depression may masquerade as irritability, over-concern about minor physical symptoms, and in organic confusional states a lethal depressive component is often latent. Early dementia and toxic states are frequent among those patients who attempt suicide and are also found to have a high risk of subsequent suicide. Other patients with mental disorders it is necessary to appraise with caution are chronic alcoholics at the end of their tether, early schizophrenics, and hysterics. Psychoneurotics other than hysterics are less often found to have serious intent. The same is true of people with psychopathic personalities, though suicidal threats and gestures recur in these cases. Other factors besides diagnosis which are helpful in distinguishing a patient in the

[1] See *Brit. med. J.*, 1961, **2**, 460.
[2] *H.M. (61) 94 and E.C.N. 375.*
[3] Stengel, E., and Cook, N. G., *Attempted Suicide*, 1958, Maudsley Monographs No. 4, London.
[4] Shneidman, E. S., and Farbarow, N. L., *The Cry for Help*, New York (in press).
[5] Schmidt, E. H., O'Neal, P., and Robins, E., *J. Amer. med. Ass.*, 1959, **168**, 549.
[6] Batchelor, I. R. C., and Napier, M. B., *Brit. med. J.*, 1953, **2**, 1186.
[7] Sainsbury, P., *Proc. roy. Soc. Med.*, 1961, **54**, 266.
[8] Robins, E., Murphy, G. E., Wilkinson, R. H., Gassner, S., and Kayes, J., *Amer. J. publ. Hlth*, 1959, **49**, 888.
[9] Capstick, A., *Brit med. J.*, 1960, **1**, 1179.
[10] Ibid., 1961, **1**, 1067.
[11] O'Neal, P., Robins, E., and Schmidt, E. H., *Arch. Neurol. Psychiat. (Chicago)*, 1956, **75**, 275.

severe category are, in the elderly especially, the presence of physical illness, recent bereavement, and loneliness. Of less serious implication, particularly in the young, are marital, family, and lovers' quarrels.

These observations suggest the outline of a programme for the management of attempted suicides. After the period of surgical or medical danger has passed the first step will be to decide from an examination of the patient's mental state, from his attitude to suicide and his future, and from the history and circumstances of the attempt whether it can confidently be classified as a serious one or not. When there is any doubt about the suicide intention a psychiatric opinion should be sought. The serious cases will usually require admission to a psychiatric unit. It is of interest to remark here that the suicide rate in mental hospitals has remained steady at about 50 per 100,000 residents, which is low considering the vulnerability of the population. Recently, since the introduction of the open-door policy, the rate has decreased considerably. It is probably important, therefore, not to take precautions against suicide to the point of jeopardizing the liberal atmosphere of the hospital. Fortunately the majority of patients requiring admission will be suffering from depressive illnesses and therefore readily amenable to treatment. Those with physical illnesses, organic psychoses, and those elderly patients with apparently minor physical disabilities which often assume great importance if they restrict the old person's activities and independence need the full facilities of the general hospital.

When the patient's and his relatives' or friends' account of the attempt have been evaluated, domestic and other environmental stresses which culminated in or contributed to the suicide act need to be remedied in a practical manner where possible, and the patient will need help to acquire some insight into his problems so that he can cope with them more realistically. All this should be part of a co-ordinated policy carried out by psychiatrist, general practitioner, and social worker. Patients seen by the general practitioner and not admitted to hospital as well as those discharged from hospital ward or casualty department will need further medical and social support sometimes either from their own doctor or from the psychiatric services. A clear arrangement should be made with one or the other, for it is important that the patient should know whom he can turn to for help until the crisis in his affairs is past. A psychiatric social worker can help in co-operation with the doctor when the social and family situation demands it. She might, for example, examine the needs of a lonely old woman and help her to obtain some of these, or advise an unemployed person on the financial crises which apparently precipitated the attempt, or more simply help the patient and his family by providing reassurance and explanation about the nature of the illness he has been suffering from. A simple planned procedure of this kind could be a useful step forward in the field of preventive and community psychiatry.

CARCINOMATOUS SYNDROMES

During recent years much interest has been aroused by reports of a variety of syndromes occurring in association with neoplastic disease—both carcinoma and malignant lymphoma—which are not due to infiltration by the tumour or its metastases. As the number of cases grows it is also apparent that the site of the primary tumour is seldom important, except perhaps in special instances such as hypertrophic pulmonary osteoarthropathy and polycythaemia. There is nevertheless a preponderance of certain types of neoplasm in some of the syndromes, such as the association of intrathoracic tumours with adrenocortical overactivity and gastrointestinal carcinoma with vascular thrombosis, though this may reflect the incidence of certain tumours rather than a direct aetiological relationship. These syndromes are of great theoretical interest for the questions they pose on mechanisms of cancer, but they also have a practical importance in alerting the physician to the presence of a primary tumour which may well be treatable.

One of the best known and certainly the oldest is thrombophlebitis migrans. First described by Trousseau, who is said to have suffered from painful attacks of superficial thrombophlebitis and later to have died of a carcinoma of the stomach, the condition was at one time believed to be associated with pancreatic carcinoma. It is now considered to occur with any kind of cancer, and its appearance should warn the physician to make a thorough search for malignant disease, according to a recent report from Irving S. Wright and colleagues.[1] A theory that the vascular changes were due to liberation of pancreatic enzymes into the circulation has received little experimental support, and the association with a variety of carcinomata renders such a view untenable. It is now recognized also that major veins and even arteries can be affected, with resultant infarction of organs such as the brain, and in addition non-bacterial vegetations can arise on the heart valves, which are sometimes themselves the origin of systemic emboli.[2] Obviously the distinction of such vascular lesions from tumour emboli may be possible only at necropsy.

Much attention has been devoted to the neurological syndromes associated with neoplasia.[3-5] Of these the commonest are cerebellar cortical degeneration, peripheral neuropathies, and neuromuscular disorders, which may occur either singly or in various combinations. Cerebellar symptoms tend to run an acute course, while the neuropathies—often predominantly motor—may appear several years before the neoplasm is detected and have been known to remit completely. Syndromes resembling motor-neurone disease, myopathies, and myasthenia gravis have also been described, the latter responding to neostigmine.[6] Mental changes resembling dementia or psychosis may tax the diagnostic skill of the clinician. Histological examination reveals degeneration and demyelination of affected areas; and similar changes, which cannot be ascribed to treatment with radiotherapy or cytotoxic drugs, have been found in patients with myeloma, Hodgkin's disease, lymphatic leukaemia and lymphosarcoma.[7 8] It is convenient to include dermatomyositis in this group, since severe weakness especially of the bulbar muscles may simulate a neurological disorder. It has been estimated that a neoplasm is present in about 15% of cases,[9 10] and it may be so small as to be undetected during life.

A third group of syndromes may be loosely termed the endocrinopathies. Hyperfunction of the adrenal cortex, especially in association with oat-celled carcinoma of the bronchus and with tumours of the thymus, is being increasingly recognized.[11-16] Clinical evidence of Cushing's syndrome is often lacking, but blood and urinary levels of corticosteroids are extremely high, and hypokalaemic alkalosis, which is a feature of aldosteronism but is uncommon in Cushing's syndrome, may be present. When aldosterone levels have been measured, however, they have been normal. At necropsy the adrenals are found to be enlarged while the pituitary is normal, but it is not yet known whether the tumour itself secretes cortical hormones or a substance with corticotrophin-like activity or whether it influences adrenal function in a more indirect manner. There is an opportunity here not only for assay of tumour material but also for a wide-scale investigation of adrenal activity in patients with carcinoma.

Less well known is the occurrence of hypercalcaemia in the absence of bony metastases.[17] Here again the condition may mimic hyperparathyroidism, though parathyroid-like activity has not been found in tumours examined. But the amount of calcium bound to protein in the serum is increased, perhaps because of a substance produced by the tumour. An alternative theory is that increased sensitivity to vitamin D leads to increased absorption of calcium, a mechanism that is known to occur in sarcoidosis. Whatever the cause, health is restored by removal of the tumour, and cortisone will suppress the hypercalcaemia. Somewhat similar is the occurrence of hypoglycaemia with tumours which do not involve the pancreas or liver,[18] though this may represent a special rather than a general phenomenon, as is almost certainly the case with the association of polycythaemia and renal tumours.[19] Finally the occurrence of gynaecomastia, spider naevi, and palmar erythema in some patients with carcinoma or malignant lymphoma is suggestive of a disturbance in oestrogen metabolism.

A number of other syndromes have been described—for example, acanthosis nigricans, ichthyosis, secondary amyloidosis, and sarcoid-like lesions in glands.[20] Such indeed is their variety that it is impossible in the present state of knowledge to do more than speculate on how they might arise. Thus nutritional and metabolic factors have been invoked, with defects in enzyme systems affecting multiple tissues: a similarity has been noted between the neurological changes induced by vitamin-B_{12} deficiency and those of carcinomatous neuropathy. The cachexia that accompanies neoplastic disease has not yet been adequately explained. Hormonal disturbances are self-evident in some syndromes, and might be looked for more thoroughly in others. A viral aetiology has been suggested to explain certain features, and the well-known association of herpes zoster with malignancy quoted in support. More plausible, however, seems some form of hypersensitivity, perhaps vascular, or autoimmune process. The vascular and neurological syndromes could be explained on this basis, as well as dermatomyositis, "sarcoidosis," and the occasional development of a rheumatoid type of arthritis. W. Dameshek and colleagues[21] have put forward the view that the haemolytic anaemia that sometimes accompanies the

[1] Lieberman, J. S., Borrero, J., Urdaneta, E., and Wright, I. S., *J. Amer. med. Ass.*, 1961, **177**, 542.
[2] McDonald, R. A., and Robbins, S. L., *Ann. intern. Med.*, 1957, **46**, 255.
[3] Brain, W. R., and Henson, R. A., *Lancet*, 1958, **2**, 971.
[4] Smith, W. T., *Postgrad. med. J.*, 1961, **37**, 282.
[5] Holt, G. W., *Amer. J. med. Sci.*, 1961, **242**, 93.
[6] Anderson, H. J., Churchill-Davidson, H. C., and Richardson, A. T., *Lancet*, 1953, **2**, 1291.
[7] Cavanagh, J. B., Greenbaum, D., Marshall, A. H. E., and Rubinstein, L. J., ibid., 1959, **2**, 524.
[8] Lloyd, O. C., and Urich, H., ibid., 1959, **2**, 529.
[9] Dowling, G. B., *Brit. J. Dermatol.*, 1955, **67**, 275.
[10] Williams, R. C., Jr., *Ann. intern. Med.*, 1959, **50**, 1174.
[11] Aikott, E. N., and Skelton, M. O., *Lancet*, 1960, **2**, 278.
[12] Bagshawe, K. D., ibid., 1960, **2**, 284.
[13] Christy, N. P., ibid., 1961, **1**, 85.
[14] Hills, A. G., and Woeber, K. A., *Ann. intern. Med.*, 1961, **54**, 1295.
[15] Billinghurst, J. R., Thould, A. K., Galpin, O. P., and Hinton, J. M., *Brit. med. J.*, 1961, **2**, 490.
[16] Ibid., 1961, **2**, 505.
[17] *Ann. intern. Med.*, 1961, **54**, 1026.
[18] Lowbeer, L., *Amer. J. clin. Path.*, 1961, **35**, 233.
[19] Damon, A., Holuh, D. A., Melicow, M. M., and Uson, A. C., *Amer. J. Med.*, 1958, **25**, 182.
[20] Gresham, G. A., and Ackerley, A. G., *J. clin. Path.*, 1958, **11**, 244.
[21] Dameshek, W., Schwartz, R., and Oliner, H., *Blood*, 1961, **17**, 775.

malignant lymphomata may represent an immune reaction by the body to the abnormal "foreign" lymphomatous tissue, and some carcinomatous syndromes may be similar. Nevertheless it seems unlikely that a single explanation can suffice for such a diversity of pathological conditions. Though admittedly uncommon, these syndromes present an opportunity for investigation by modern pathological techniques, which could perhaps furnish a clue to the mechanism of cancer itself.

VIRILIZING ACTION OF PROGESTOGENS ON THE FEMALE FOETUS

The possibility of causing masculinization of the female foetus by treating pregnant women with oral progestogens was discussed in a leading article last year.[1] It is clear that, though uncommon, this is a definite, even if not generally serious, risk to be faced. It also seems clear that some progestogens are more likely to have this virilizing action than others, so that preliminary testing to detect this tendency is highly desirable. G. K. Suchowsky and K. Junkmann[2] have described a series of animal assays which appear to give the kind of information needed to help the clinician in his choice of progestogen for therapy in pregnant women. They measured and compared, first, the progestational activity by means of the Clauberg test on the rabbit uterus (this, unfortunately, does not necessarily parallel activity in the human); secondly, the androgenic activity, using the weight of the seminal vesicles of spayed rats and the growth of the chick comb; and, thirdly, the virilizing activity during pregnancy, using female rat foetuses. It is this last test that provides critical information for the purpose under consideration. The compounds to be tested were administered subcutaneously from the sixteenth to the nineteenth days of pregnancy, and the foetuses were removed on the twentieth day. The male foetuses were discarded; in the female foetuses the anogenital distance was measured and cross-sections of the pelvis were removed for microscopic study of the development of the vagina. In all, 13,600 female foetuses were used.

From these studies they concluded that only the 17α-hydroxyprogesterone derivatives—such as the caproate ("primolut depot")—showed no masculinizing tendencies, even when given in very high dosage. On the other hand, they found that alkylation of 17α-hydroxyprogesterone derivatives could lead to virilizing activity: 6α-methyl-17α-hydroxyprogesterone acetate ("provera"), though of comparable progestational activity and showing only slight androgenic activity, had a marked virilizing effect on the female foetus—almost as much as testosterone propionate. This demonstrated clearly that the virilizing properties of a steroid, as defined above, do not necessarily run parallel with its androgenic activity. Among the 19-nor-17α-alkyl testosterone derivatives, 17α-methyl-19-nortestosterone ("orgasterone"), though a potent progestogen, also showed marked androgenic and virilizing activity; the 17α-ethinyl compound ("primolut N") and its acetate were less androgenic and virilizing, but showed both these effects in high doses. 17α-Ethinyl-$\Delta^{5(10)}$-androstene-17β-ol-3-one (norethynodrel, the progestogen in "enavid"), though slightly less androgenic than the two previous steroids, showed a more pronounced virilizing action on the female foetus. In the case of 17α-allyl-19-nor-Δ^4-androstene-17β-ol ("gestanin") rather weak progestational activity (in the Clauberg test) was combined with a notable discrepancy between the weight changes in the seminal vesicle (there was no increase) and the chick-comb test, which gave a steep regression line. In sufficiently high doses this compound also had a virilizing action on the female foetus, and though Madjerek and colleagues[3] state that when it was given by mouth foetal virilization was not observed Suchowsky[4] could find little difference between the effects of oral and of subcutaneous administration.

The important, but unfortunate, fact that emerges from these studies is that none of the oral progestogens tested was entirely free from virilizing effects on the female rat foetus. Those who fear the possible consequences to the foetus of progestational therapy in women during pregnancy should therefore consider abandoning oral therapy and rely on parenteral treatment with 17α-hydroxyprogesterone esters.

[1] *Brit. med. J.*, 1960, **2**, 723.
[2] Suchowsky, G. K., and Junkmann, K., *J. clin. Endocr.*, 1961, **68**, 341.
[3] Madjerek, Z., de Visser, J., van der Vies, J., and Overbeek, G. A., *Acta endocr. (Kbh.)*, 1960, **35**, 8.
[4] Suchowsky, G. K., unpublished data.

ANTIBIOTICS IN INFANTILE ENTERITIS

Outbreaks of infantile enteritis due to pathogenic types of *Escherichia coli* may still assume serious proportions and present problems in control and treatment. An example of such an epidemic is described by H. Hanssler,[1] of the Children's Clinic, Regensburg: 202 infants were attacked during a six-month period, of whom 19 died, 16 of these being premature infants. It is mentioned that the sister in charge of the unit, five nurses, and five of the laundry personnel were found to be carriers of the prevalent type of *E. coli*, which was O111 B4. Treatment with sulphonamides was unsuccessful, and the organism was found to be resistant *in vitro* to chloramphenicol, streptomycin, tetracycline, erythromycin, and neomycin, an ominous illustration of the capacity of some kinds of bacteria to evade the successive attacks of antibiotic therapy. It was then noticed that infants who were being given "inacil" for the prevention of staphylococcal infection were escaping the prevailing epidemic of enteritis. A capsule of this preparation of the size given to infants contains 50 mg. of novobiocin and 50,000 units of penicillin V. This was accordingly tried for the treatment of subsequent cases of enteritis, with what is claimed to have been remarkable success. Two detailed charts are given showing this effect, first in an infant previously treated unsuccessfully with sulphaguanidine and several anti-

[1] Hanssler H., *Dtsch. med. Wschr.*, 1961, **86**, 1517.
[2] Garrod, L. P., *Brit. med. J.*, 1960, **2**, 1695.

biotics, and, secondly, in one treated with inacil *ab initio*: they show cessation of fever and diarrhoea and rapid resumption of a steady gain in weight. The organism was eliminated from the stools in 80% of the treated infants. Polymyxin and colistin were given to some of the infants, apparently with benefit, although the effect was less rapid: they sometimes abolished the subsequent carrier state when inacil had failed to do so.

Neither of the two antibiotics in inacil is one which would be expected to exert much effect in an infection of this nature. The only coliform bacillus usually regarded as sensitive enough to novobiocin to encourage its therapeutic use is *Proteus*, and although the strain of *E. coli* in the Regensburg outbreak was "sensitive" to novobiocin the inhibitory concentration is given as 50 μg./ml., which certainly indicates no very hopeful degree of sensitivity. Coliform bacilli have simply been dismissed in the past as resistant to penicillin, and although in fact some strains of *E. coli* are killed by fairly high concentrations attainable in such areas as the urinary tract this applies chiefly to penicillin G: penicillin V, which inacil contains, is even less active against this species.[2] It is conceivable that these two antibiotics may have some unexpected synergic effect, but the author of this paper mentions no attempt to demonstrate it *in vitro*. His observations therefore remain unexplained, and must await verification and perhaps elucidation by others.

INFECTIVE HEPATITIS AND CHIMPANZEES

The study of viral hepatitis has been seriously handicapped by the inability to transmit the disease to any animal species other than man.[1] Nevertheless the use of human volunteers has clearly established that the causative agent has the properties of a virus, exists in the blood stream both during and for a variable period after clinical disease, and is excreted in the upper respiratory passages and in the faeces. It is therefore not surprising that in the majority of epidemics that have been adequately investigated transmission has been shown to have resulted from contamination of water, milk, or food by patients or carriers of the virus. A recent report by W. D. Hillis[2] of a series of cases among personnel handling young chimpanzees at a United States Air Force base has for the first time provided strong evidence that an animal reservoir can occasionally be the source of a new epidemic.

Among the animals maintained for experimental purposes at the Holloman Air Force Base, New Mexico, is a colony of about 40 chimpanzees. These are obtained from two principal sources: the majority from commercial vendors in West Africa, the remainder from a game farm near Miami, Florida. The newly arrived animals are kept isolated from the main colony for 45 days, and the isolation unit is under the care of veterinary surgeons and their staff. Between 1958 and 1960 the annual incidence of viral hepatitis in the county in which the base is situated ranged between 0.3 and 1.8 per thousand. The incidence of the disease during the same period at the base hospital at Holloman, which is responsible for the care of a population of about 6,500, was, excluding members of the Veterinary Services Branch, also about 1.8 per thousand. But among the 21 individuals who as a result of their job were exposed to intimate contact with the newly arrived chimpanzees there were nine clinical and two subclinical cases of hepatitis between August, 1958, and October, 1960. In each clinical case the period between exposure and the appearance of the disease lay between two and six weeks, the accepted incubation period of infective hepatitis. As the members of the Veterinary Service shared all the amenities of the base the only known significant difference between them and other personnel was the contact with the chimpanzee colony. Since, moreover, no case of hepatitis occurred among those responsible for the established colony the increased incidence of the disease was apparently directly associated with the handling of the newly arrived animals.

Despite the extremely careful examination of all the newly acquired animals and necropsy of those that died in captivity no suggestion of hepatitis was found in any of them. It was, however, established that one of the vendors in West Africa gave all his chimpanzees several intraperitoneal injections of pooled human blood in the hope that this might reduce their susceptibility to the various human diseases to which captivity would expose them. It seems highly probable that in some of these animals virus present in the pooled human blood survived in a form capable of transmitting the disease to human recipients. As many of those handling the young chimpanzees are often bitten or scratched by their charges it is impossible at present to say whether the infection was transmitted by direct inoculation or by the more usual oral route through faecal contamination.

GUY FAWKES STILL A THREAT

Careless handling of fireworks can cause appalling injuries. Some of those treated at the Birmingham Accident Hospital are illustrated in Mr. Douglas Jackson's warning article at p. 1184 in this issue. "Few anniversaries," he writes, "can be accompanied by such a trail of injury and suffering throughout the length and breadth of the country." What can be done to reduce this toll? First of all some fireworks can be made safer: the taming of the "banger," for instance, has done much to prevent blast injuries of the hands, and the manufacturers have agreed among themselves to ban those type of fireworks which have proved specially dangerous. Secondly, as Mr. Jackson says, the press has helped to educate the public by emphasizing the dangers of, for instance, holding fireworks in the hand or of putting them in a pocket. But though this and other means of educating children and parents must have done good, no decline in casualties has been seen in Birmingham over the years. Thirdly, some control of

[1] MacCallum, F. O., McFarlan A. M., Miles, J. A. R., Pollock, M. R., and Wilson C., *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 273, 1951, p. 135.
[2] Hillis, W. D., *Amer. J. Hyg.*, 1961, 73, 316.

[1] *Brit. med. J., Supplement*, 1961, 2, 88.
[2] *United Kingdom Fire Statistics, 1960*, H.M.S.O., London, 1961. Price 12s. 6d. net.
[3] *Brit. med. J.*, 1960, 2, 1375.

the sale of fireworks might be contemplated. A resolution that the Representative Body of the B.M.A. should recommend that the sale of fireworks to the public be prohibited was defeated at the A.R.M. this year on the grounds that this was too drastic.[1] Mr. Jackson suggests that safety could be achieved by restricting fireworks to organized displays: in his opinion nothing less than this will reduce "the disgraceful and unnecessary suffering of the Guy Fawkes celebration year after year." No doubt if many parents saw, as Mr. Jackson sees, the burned children being brought into the casualty departments of hospitals on and around November 5 they might agree with him. But as it is most parents feel that they are capable of preventing their own children from being injured in the back-garden firework displays which they probably remember as an exciting treat in their own childhood days. What might help for a start is effective supervision—perhaps by voluntary wardens—of all the bonfires which boisterous gangs of children love to start on their account once they have filled their pockets with "pennies for the guy." Fire brigades—which dealt with 892 fires caused by explosives or fireworks last year[2]—often send out patrols to keep an eye on bonfires, but it is impossible to have a fireman on hand all the time.

While prevention is all-important in reducing the number of serious casualties on Guy Fawkes night, efficient first-aid treatment can help to reduce the pain and disability caused by any firework injury. Some advice on this was given in this journal a year ago.[3]

NURSING-HOMES

The registration and inspection of nursing-homes is a duty laid upon local authorities by the Public Health Act of 1936. For many years medical officers of health have found the law on the subject unsatisfactory, and a recent report[4] published by the National Corporation for the Care of Old People shows how much confusion and ambiguity there is in existing legislation. The definition of a nursing-home is itself vague and depends largely on "the providing of nursing." Thus various types of homes, such as convalescent homes or homes for the disabled, could be included, though in practice local authorities exclude them. On the other hand, many nursing-homes cater now almost exclusively for old people yet are often indistinguishable from private old people's homes, which are required to register under the National Assistance Act, 1948. The number of such homes is increasing more rapidly than that of nursing-homes, and the authors of the report suggest that it may be easier to obtain registration under the National Assistance Act than under the Public Health Act if facilities are poor and the proprietor has no nursing qualifications.

Two of the four conditions under which registration may be refused or cancelled depend on the undefined word "fit" applied to the person carrying on the home or to the premises used: it is left to the discretion of the local authorities to interpret this term. But it may be difficult to prove to the satisfaction of a court that an applicant is not fit to carry on a nursing-home and virtually impossible to do so when cancellation of an existing certificate is under consideration—all the more as some homes are run technically by a company. Standards and amenities within the home itself may deteriorate with the course of time or may not be adapted to the changing pattern of nursing care. Most old people now spend at least part of the day sitting up in a chair, yet may not even have a small table on which their meals can be served, not to speak of a sitting-room in which they can relax with others. The medical officer of health lacks the necessary powers to enforce a remedy for this and other shortcomings. Nevertheless the majority of nursing-home proprietors are willing to accept his advice, even if only in the mistaken belief that he has the right to require them to do so. But in the face of opposition he can apply only the ultimate sanction of the threat of cancellation of registration.

The report states that in England and Wales there were nearly 1,600 registered nursing-homes in England and Wales with just under 18,700 beds (1,600 maternity). The average number of nursing-home beds was at least 5 for every 10,000 of the population, but in towns like Bournemouth and Eastbourne the number was much higher. At least 114 voluntary homes (5,500 beds) are granted exemption from registration, and therefore from inspection, on the grounds that they are not carried on for profit. The reason for this clause in the Public Health Act is lost in antiquity. There is no such exemption for voluntary mental nursing-homes under the Mental Health Act, 1959. Indeed, this Act provides stringent rules for registration and inspection, and regulations issued in July, 1960, prescribe in detail the information which a prospective proprietor must supply to the local authority. A series of fines can be imposed for infringement of the conditions of registration before resort to cancellation becomes necessary.

There may be little support for the proposal in the report that a regional inspectorate should be set up for all health and welfare eestablishments not owned and managed by regional hospital boards or local authorities. The effectiveness of the supervision of nursing-homes exercised by medical officers of health depends on the powers given to impose conditions and to see that they are carried out and not on the number of homes registered and inspected annually by the local authority. What is needed is a change in the law giving powers to the local authorities to impose penalties for infringement of the conditions of registration, or, alternatively, to register homes for a fixed period, after which fresh application would have to be made. Local authorities and the Society of Medical Officers of Health have been pressing for changes in the legislation for many years. They are long overdue.

The next session of the General Medical Council will open on Tuesday, November 21, at 2.15 p.m., when the President, Sir David Campbell, will take the chair and will deliver an address.

[4] Woodroffe, Caroline, and Townsend, P., *Nursing Homes in England and Wales—A Study of Public Responsibility*, 1961. National Corporation for the Care of Old People, Nuffield Lodge, Regent's Park, London W.1. Price 7s. 6d.

Clinicopathological Conference

A CASE OF RENAL FAILURE

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a man who developed acute renal failure, and died at Hammersmith Hospital after transfer there for haemodialysis (Case No. 239,754; P.M. No. 9,247).

Clinical History

Dr. M. D. MILNE: This patient was a man aged 62 at death. In 1914 he had had acute glomerulonephritis but appeared to have made a complete recovery. He stated he had had rheumatoid arthritis for twenty years, and had been treated with gold injections. In the last few years the arthritis had improved, and there was very little residual pain, stiffness, or deformity. In February, 1959, he attended the out-patient department of another London teaching hospital complaining of flatulence, headache, diarrhoea, and polydipsia. The urine at that time contained a trace of protein. Barium enema *x*-ray showed a solitary diverticulum in the transverse colon.

RENAL FAILURE

He re-attended the same out-patient department a year later, and now complained of severe polydipsia and polyuria, with general weakness, nausea, and paraesthesiae of the fingers. There was now gross proteinuria but nothing else abnormal was found on physical examination. The blood pressure was 135/90. He was admitted to the hospital on April 28, 1960. There was some anaemia, the haemoglobin being 11 g./100 ml., but the white cell count and differential were normal. The erythrocyte sedimentation rate was raised, being 58 mm. in one hour. The blood urea was 210 mg./100 ml., plasma sodium 141, and plasma potassium 6.6 mEq./l. Serum calcium was 8.7 mg./100 ml., and the total serum protein 6.4 g./100 ml., with a high alpha$_2$-globulin peak on electrophoresis. The urinary output was less than one litre per day, and the urinary specific gravity was 1007. There were erythrocytes and a few casts in the urinary deposit. *X*-ray of the skull was normal, but chest *x*-ray showed a shadow in the left hilar region. *X*-ray of the abdomen showed that the kidneys were normal in size and position. The volume of urine remained less than one litre per day despite a liberal fluid intake. After he had been in hospital for ten days (on May 8) the serum potassium rose to 9.3 mEq./l., and he developed respiratory distress and a flaccid quadriplegia. He was treated with insulin injections, intravenous calcium gluconate, and oral cation-exchange resins in the sodium phase. Power returned to his limbs after six hours of this treatment.

On the next day (May 9) the plasma sodium was 126 mEq./l., the plasma chloride 91 mEq./l., and the plasma potassium had fallen to 6.6 mEq./l. It was thought safer to treat him by haemodialysis and he was transferred to Hammersmith Hospital.

HAEMODIALYSIS

On admission he was obviously a very ill man with generalized twitching of limbs, but the Chvostek and Trousseau signs were negative. There was considerable hyperpnoea but no increase of jugular venous pressure. The heart was enlarged to the left and the blood pressure was 140/80. Crepitations were heard at both lung bases, the liver was not palpable, but the kidneys were both palpable and felt normal in size. There was no peripheral oedema, the bladder was not distended, and the prostate was not enlarged. There was no swelling or deformity of joints, but crepitus and some stiffness were present in all the large joints of the limbs. There were no palpable lymph glands.

Blood urea was 390 mg./100 ml., plasma potassium 7 mEq./l., plasma sodium 116 mEq./l., plasma bicarbonate 11 m.mol./l., serum calcium 10 mg./100 ml., and urinary specific gravity was 1016. Some erythrocytes and cellular casts were present in the urinary deposit but culture of the urine was sterile. The electrocardiogram showed raised ST segments in leads I, II, VL, VF, V_5 to V_7, and depressed ST segments in leads V_4R, V_1, V_2, and V_3. The T waves and the QRS complexes were both normal. On straight *x*-ray of the abdomen the kidneys appeared to be somewhat increased in size. A chest *x*-ray showed moderate generalized cardiac enlargement and both hila were enlarged, the left more than the right. The haemoglobin was 9.4 g./100 ml., serum albumin 3.4 g./100 ml., and serum globulin 3.2 g./100 ml., with an increase of alpha$_2$-globulin on electrophoresis. The plasma cholesterol was 200 mg./100 ml., plasma fibrinogen 480 mg./100 ml., plasma bilirubin 0.5 mg./100 ml., plasma alkaline phosphatase 10 K.-A. units/100 ml., and the serum antistreptolysin 25 units/ml. A Congo-red test showed a 70% clearance of the dye from plasma within 30 minutes.

He was now almost completely anuric and was treated both with the conservative regime for acute renal failure and by haemodialysis with a Kolff rotating-coil artificial kidney. He developed severe hypotension during the first dialysis and the treatment had to be stopped after two hours. Six days after admission his condition had deteriorated and peritoneal dialysis was attempted, but there was only a slight fall of blood urea. Three days later his blood urea had risen to 615 mg./100 ml. and haemodialysis was attempted for the second time. He again became severely hypotensive and shocked, and treatment was stopped after three hours. He died shortly afterwards, on May 18.

Guest Speaker: Professor A. Kekwick

Professor J. MCMICHAEL: We have invited a distinguished visitor, Professor Alan Kekwick, from the Middlesex Hospital, to discuss this case, without having told him our diagnosis.

ACUTE RENAL FAILURE

Professor A. KEKWICK: I would like to thank you very much for asking me here, although I feel fearful of the ordeal awaiting me. It is a little difficult to know where to start with this mass of data, but I would like to try and start in the period between April 28 and May 9—a period for which a lot of information is

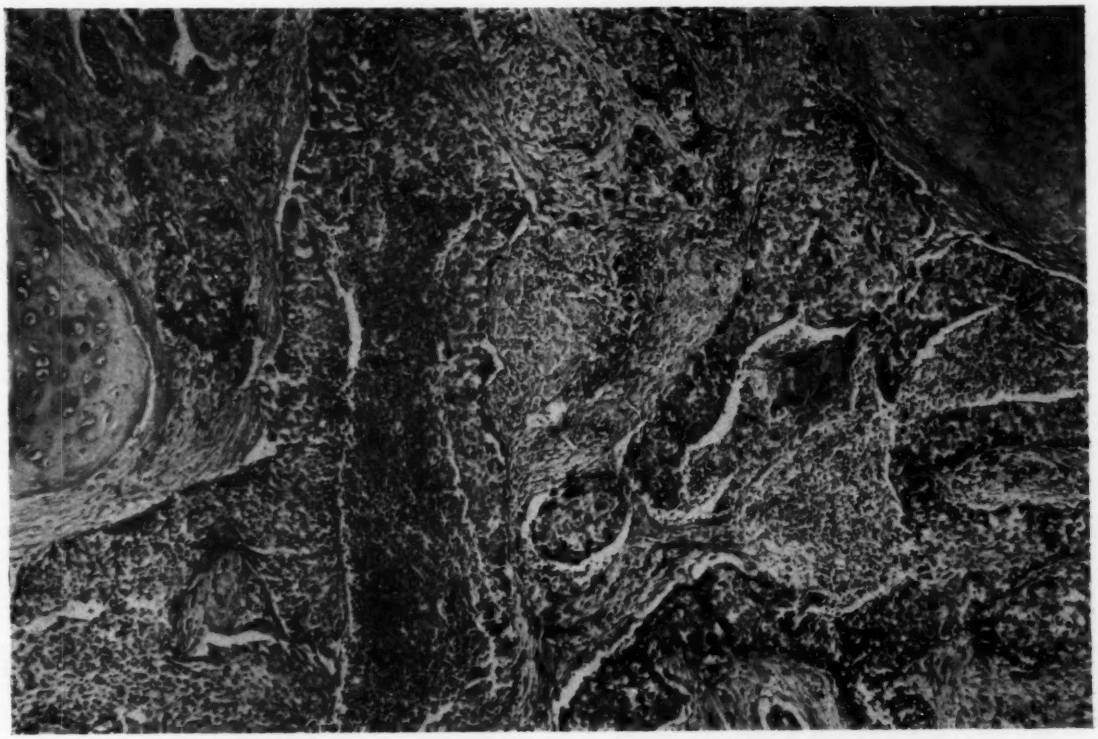


FIG. 1.—Wall of bronchus infiltrated by an anaplastic carcinoma. (H. and E. ×84.)

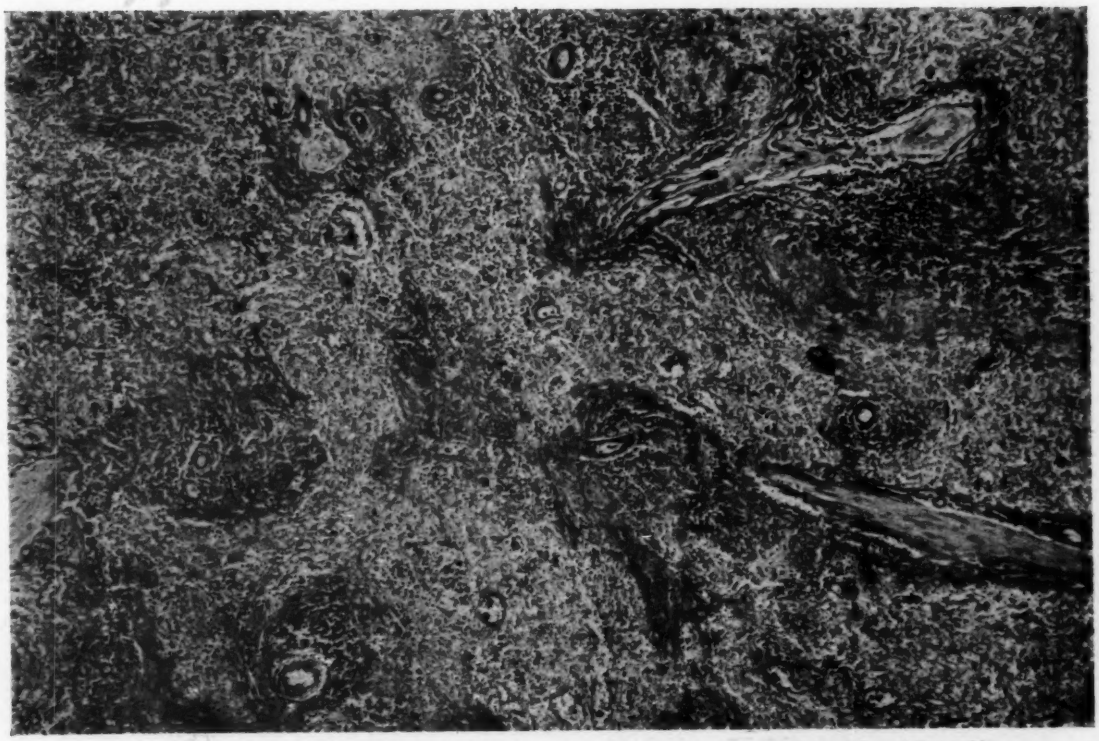


FIG. 2.—Spleen showing deposits of amyloid (dark grey) around arteries and trabeculae. (H. and E. ×84.)

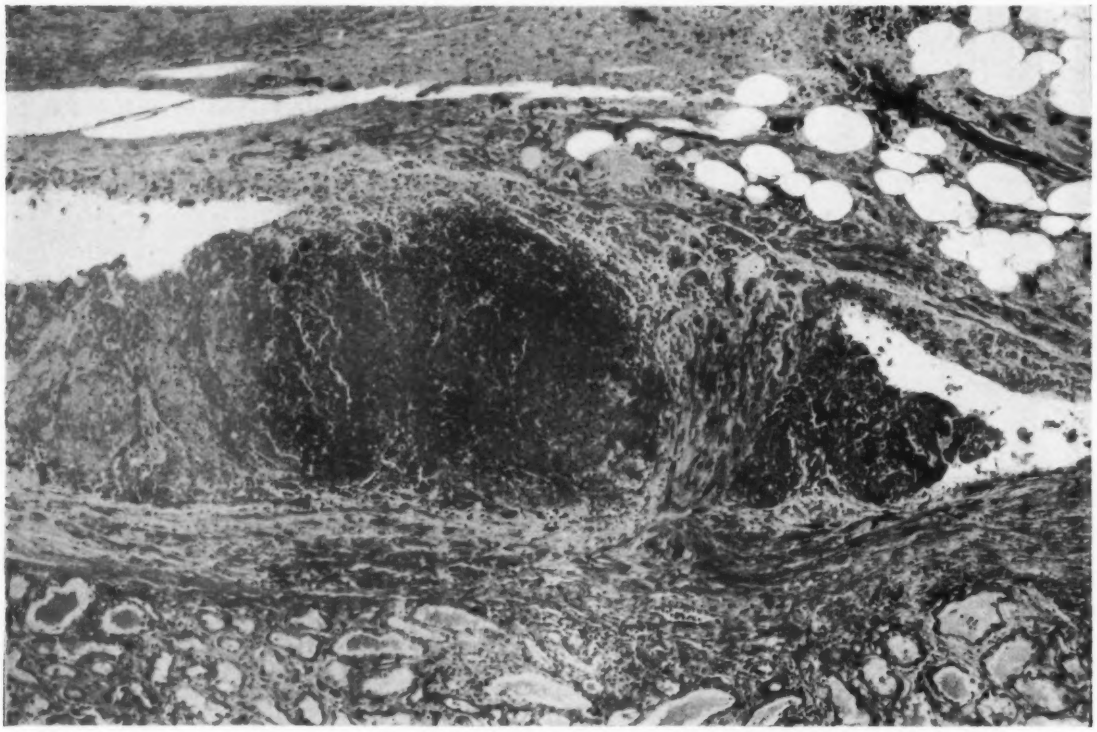


FIG. 3.—Kidney showing a partly organized thrombus in a renal vein. (H. and E. ×84.)

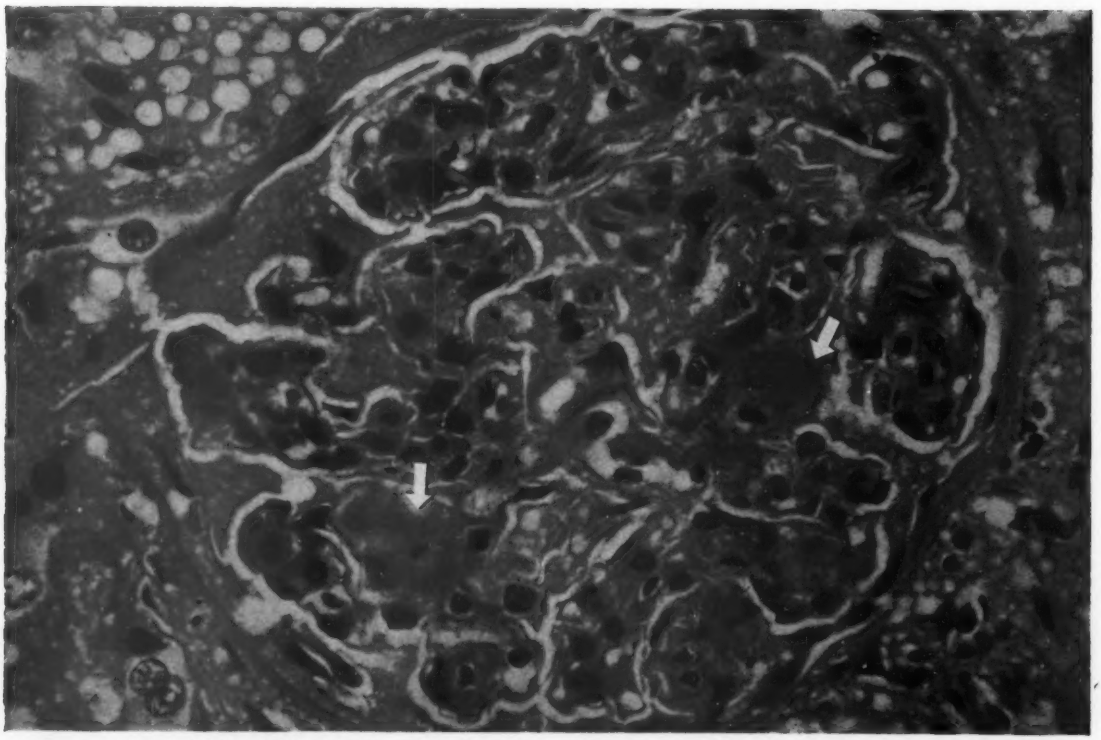


FIG. 4.—High magnification of a glomerulus showing deposits of amyloid (arrows). (H. and E. ×620.)

supplied. There seems little doubt that this was in fact the time in which the fatal illness of this man commenced, and little doubt that he died of renal failure. On April 28, for example, he had a blood urea of 210 mg./100 ml., and by May 9 it had risen to 390 mg./100 ml. These urea figures are not very high in contrast to the serious clinical state of the patient, and indicate, I think, that the onset of renal failure had been fairly rapid. There are certain other features which confirm the existence of renal failure. The bicarbonate level of 11 m.mol./l. is very low, and, although the patient is stated to be hyperpnoeic, I do not think one can get such a low figure from hyperpnoea alone, but a pCO_2 would have been very helpful at this stage. I have assumed this represents a metabolic acidosis consequent upon his renal failure.

If we turn next to the hydrogen-ion balance during this period we find that in April at some time unspecified he had 141 mEq./l. of sodium, on May 9 this had dropped to 126 mEq./l., and later that day this had dropped still further to 116 mEq./l. The chloride figure given for May 9 is 91 mEq./l. while the bicarbonate is 11 m.mol./l.—a total of 102 mEq., as against a figure for sodium of 126 mEq., a gap of 26 mEq./l. This is the usual figure and can be interpreted to mean that this patient was struggling with his hydrogen-ion balance and that no other type of acid had been introduced into the blood. This completes the full metabolic picture of the disturbance found in renal failure.

Potassium Levels

We come next to the potassium figures of which we have two which I think are important. On May 8 the serum potassium rose to a figure of 9.3 mEq./l., dropping on the next day to 6.6 mEq./l. On May 8 it is said that he had a quadriplegia (I have assumed this was a flaccid quadriplegia), with alteration of his respiration. A day later, on May 9, he is said to have been twitching.

On May 8 he probably had a high serum potassium both inside and outside the nerve cells, conditions under which the nerves become depolarized, giving rise to generalized paresis, particularly in the respiratory muscles. Between May 8 and 9 sodium had probably passed into the cells and the conditions favouring hyperexcitability had been produced. This is suggested by the sodium figures. Between May 8 and 9 the serum sodium dropped 10 mEq./l., but the potassium only dropped 3 mEq./l.; that is to say that during these 24 hours the patient lost about 40 mEq. of potassium and 140 mEq. of sodium. The usual explanation of such a change is that the patient has been treated with a sodium-free fluid such as glucose and that this has resulted in both dilution and a simultaneous, selective sodium diuresis. The rapid transition in this patient from flaccid paralysis to increased muscular excitability within 24 hours in my opinion favours the view that the steep drop in sodium is accounted for by its disappearance into cells. The characteristic twitching of uraemia is usually associated with sodium passing into the cells, with a relatively low potassium outside. This leaves the raised phosphorus figure which may indicate a transference of phosphorus out of the cells into the blood, or alternatively retention by the failing kidney. It is significant that if the patient died of uraemia there is no record of hypertension.

Electrocardiograms

Now if we may next turn to the electrocardiograms, I have to confess straight away that I do not really understand electrocardiograms and so I may put my foot in it, but since they have been described I suppose I must comment. What is stated is that there was a raised ST segment in leads I and II, VL, VF, and V_5 to V_7, with a depressed ST segment in V_4R, V_1, V_2, and V_3. I take it that this probably indicated postero-lateral ischaemia, probably without recent infarction in the heart. I would have thought there was no evidence in the cardiogram reflecting the high blood potassium. My own knowledge does not go beyond the usual finding of a rather sharp T wave and widening of the QRS intervals. If this is so, this may also account for the large heart which is mentioned.

Clinical Course

We turn now to the natural history of this patient's disease. The acute glomerulonephritis appears so distant in time that I have discarded it as not relevant to the present uraemia. In 1959 he was noted to have proteinuria, but this does not seem to have disturbed anybody unduly throughout the year between February, 1959, and April, 1960; the fact of its presence probably indicates that he had a renal lesion of a relatively benign character during the year 1959 and possibly longer. There then occurred a rapid deterioration of this relatively benign lesion during April, 1960, culminating in his death on May 18. My first consideration was that this might be an example of amyloid disease of the kidney. There is the associated rheumatoid arthritis, apparently largely burnt out but having been present for a number of years. Although I am inclined to mistrust Congo-red tests, I think this one was so abnormal (70% clearance from the plasma in 30 minutes) that it indicates the presence of amyloidosis. Further, we have the raised $alpha_2$-globulin in the electrophoretic strip, again a feature of amyloidosis, and with this the associated raised E.S.R. Why, then, the sudden deterioration? Dr. Milne has recorded the association of amyloidosis with thrombosis of the renal vein and the rapid deterioration in patients that goes with it. Some confirmatory evidence appears on April 28 when erythrocytes were found in the urine.

Differential Diagnosis

I considered various other possibilities: chronic nephritis or pyelonephritis with a coronary thrombosis and a drop in blood-pressure leaving a residual large heart and consequent renal failure. There is no evidence of cardiac failure which I would have expected if this had been the course of events, and there should also have been more deterioration between February, 1959, and April, 1960, if this had been the diagnosis. Lupus erythematosus must be considered in view of its association with rheumatoid arthritis, but no evidence was given of either lupus-erythematosus phenomena or antinuclear factor, and I must assume that these were looked for. Also the disease ran a rather unusually sharp course, I think, for the renal failure of diffuse lupus erythematosus, which is usually rather more chronic. Gold nephritis is possible, but there must have been a considerable gap between the administration of gold and the final deterioration of the patient in view of the fact that we are told that rheumatoid arthritis had been quiet for some time. Also against this is the fact that

gold usually produces a nephrotic syndrome with tubular damage, and in this patient there was no change in the plasma proteins or cholesterol and no gross oedema. I have therefore placed my money on amyloid disease of the kidney and terminal bilateral renal vein thrombosis.

This leaves us with one thing which is intriguing and for which this diagnosis does not offer a satisfactory explanation. There was a shadow in the chest which is alluded to twice, the first time in April, 1960, when it was unilateral, the second time in May when it had become bilateral. One has a desire for unitarianism in diagnosis, and I suppose one could say that this might have been due to amyloidosis in the lungs or in the hilar glands. My own feeling, however, is that this was an unrelated condition altogether, and my guess on probabilities would be that this might turn out to be a carcinoma of the lung with secondaries in the glands. As I say, since I have got to put a stake down, I would plump for renal amyloidosis, bilateral renal vein thrombosis, and probably a carcinoma of the lung.

Clinical Diagnosis

Dr. MILNE: Well, we thought the same as Professor Kekwick, that this was a case of secondary amyloid from rheumatoid arthritis and that the rapid deterioration was due to bilateral thrombosis of the renal veins. We interpreted the cardiogram as suggestive of uraemic pericarditis. We were a little puzzled about the lung shadows, which really had little relevance to his terminal illness, and I think the question of carcinoma was raised but this was not proved as a definite diagnosis as it seemed irrelevant to his terminal illness. Our clinical diagnosis was:

(1) Chronic rheumatoid arthritis.

(2) Renal amyloidosis with acute oliguric renal failure, probably due to renal vein thrombosis.

(3) Pulmonary oedema and possibly a carcinoma of the bronchus at the left lung hilum.

Post-mortem Findings

Professor C. V. HARRISON: This was a rather obese man, 12 st. 5 lb. (78.5 kg.) in weight, and 5 ft. 7 in. (1.68 m.) in height. There were recent surgical incisions for dialyses in the abdomen, the groins, and the elbow regions. The genital organs were oedematous, but there was no oedema elsewhere. The left index finger was ankylosed at the first interphalangeal joint. The toes were dorsiflexed at the metatarsophalangeal joints.

Cardiovascular System: The heart weighed 428 g. (normal 360 g.). It showed mild generalized hypertrophy. There was a single 5-mm. adhesion between the right coronary and the non-coronary cusps of the aortic valve. All the other valves were healthy. The heart muscle was healthy and showed no ischaemic lesion. The aorta showed average atheroma for a man of this age. Microscopy confirmed the naked-eye findings.

Respiratory System: The right lung, which weighed 675 g. (normal 450 g.), showed acute bronchitis with reddening of the bronchi. Most of the posterior basal segment showed honeycomb change, with fibrous tissue separating fairly uniform cysts about 2 mm. diameter. The left lung weighed 720 g. (normal 400 g.). At the commencement of the bronchus to the apical segment of the lower lobe there was a small carcinoma, 15 mm. in diameter. The lung distal to it showed septic bronchiectasis and lipid pneumonia. There was also oedema of the upper lobe. There was pleurisy over the consolidated part of this lung and extensive adhesions over the diaphragm. Histology: The tumour proved to be an anaplastic spheroidal cell carcinoma (Fig. 1). The purulent bronchiectasis and the endogenous lipid pneumonia were confirmed. Right lung: honeycomb lung confirmed.

Alimentary System: The oesophagus, stomach, and intestines were normal except for mild diverticulitis in the descending colon. The liver, which weighed 2,095 g. (normal 1,600 g.), was enlarged and a little pale. Microscopically it showed moderately severe periportal fatty change. No amyloid was seen.

Reticulo-endothelial System: The spleen weighed 577 g. (normal 170 g.) and was very firm. Its cut surface showed typical generalized amyloid. The iodine test was intensely positive. Microscopically there was severe amyloidosis of the Malpighian bodies, trabeculae, and Billroth cords (Fig. 2). Lymph nodes showed slight generalized enlargement macroscopically. The bone marrow was normal.

Endocrine Glands: The thyroid weighed 35 g. (normal 30 g.) and was macroscopically normal, but the iodine test was strongly positive. The adrenals were enlarged to about twice normal size and gave a strongly positive amyloid test. Sections confirmed this.

Genito-urinary System: Both kidneys were enlarged, weighing together 484 g. (normal 340 g.). Their cut surface was pale, with a wide, waxy-looking cortex, ill-defined from the medulla. Iodine gave a positive reaction in the glomeruli and in the inner part of the medulla. Thrombosis (Fig. 3) was found in veins at the arcuate level, but not proximal to this. Section showed amyloid in the glomeruli (Fig. 4), the interstitial tissue (particularly in the medulla), and in some of the vessels.

Joints: The hands could not be examined for lack of permission. The spine showed no evidence of spondylitis. The shoulder and sterno-clavicular joints were free from signs of arthritis. The second left metatarsophalangeal joint showed no evidence of rheumatoid arthritis.

Pathologist's Diagnosis

(1) Amyloid disease of kidneys, spleen, adrenals, and thyroid.

(2) Thrombosis of renal veins at arcuate level with fatal uraemia.

(3) Old rheumatoid arthritis.

(4) Carcinoma of left apical lower-lobe bronchus, with local bronchiectasis and pneumonia.

(5) Pleurisy with effusions.

(6) Old pericardial effusions.

(7) Diverticulosis.

Discussion

Professor MCMICHAEL: Although rheumatoid arthritis does produce amyloidosis, it is rarely so obviously clinically manifest. Am I right, Dr. Dixon?

Dr. A. ST. J. DIXON: When we get a patient with rheumatoid arthritis who has protein in his urine, amyloid is of course the first thing we think about; the second would be toxicity from the various drugs the patient may have been having. I would not say it is very common.

AMYLOIDOSIS IN RHEUMATOID ARTHRITIS

Professor MCMICHAEL: Does amyloidosis commonly lead to death in rheumatoid arthritis?

Dr. DIXON: No, it is a fairly common finding at necropsy, but is rarely the cause of death. I think there were only two in the series of 250 patients with rheumatoid arthritis that Professor Bywaters has followed for about fifteen years, where renal amyloid was the probable cause of death.

Professor MCMICHAEL: Yes, it is rare for "rheumatoid amyloidosis" to cause death in uraemia. Dr. Milne, perhaps you would like to sum up the problem as you saw it and see it now.

Dr. MILNE: Well, I was not entirely with you, sir, about the rarity of dying of renal disease in amyloidosis with rheumatoid arthritis. I should have thought statistically that, with the vast numbers of cases of rheumatoid arthritis, quite a number must die from secondary amyloidosis. Rheumatologists are always telling us that about 10% of the population have this disease, which would seem to make it almost a normal variant. Amyloidosis is a very rare complication of rheumatoid arthritis, but when it does occur I think the percentage which die of renal involvement is very high, and, provided the patient lives long enough, many of these patients will progress to uraemia. The uraemia may be in two forms: either it can be an acute oliguric renal failure as this one was, when the kidneys are large, as these were, and with a normal blood-pressure; or it may be a chronic uraemia associated with the fibrotic amyloid contracted kidney. In the latter case, of course, the kidneys are small and there is a polyuric uraemia, which is often associated with hypertension, but not necessarily.

The diagnosis of pericarditis in uraemia is always rather difficult to me. If you hear a pericardial friction rub a diagnosis can be made with confidence. Often, however, there are peculiar electrocardiographic changes, and I would be very interested in Dr. Shillingford's interpretation of these abnormal cardiograms; I see that he is studying them with interest.

I think it is a matter for discussion whether this amyloidosis is secondary to the rheumatoid arthritis. The arthritis was a very burnt-out disease both clinically and pathologically, but of course it was of long standing. I think we are at a loss to correlate secondary amyloid with the severity of the primary disease. I have seen gross disease which one usually associates with amyloid showing no amyloid at all at necropsy. On the other hand, you can get miserable little lesions which appear to have caused severe and generalized secondary amyloid. I think there is a very poor correlation between severity of primary disease and secondary amyloidosis. This is the typical distribution of secondary amyloid, but I always stress first that the differentiation in distribution is only statistical; here the distribution is typical of secondary amyloidosis. I think really that is all I can say.

RADIOLOGY FOR DETECTING SPLENOMEGALY

Professor MCMICHAEL: Why didn't we feel the spleen? It was about three times the normal weight.

Dr. MILNE: Perhaps because he was rather a big man. We often find radiology rather more delicate than palpation, I am ashamed to say, and I usually bow to Dr. Steiner's opinion in the diagnosis of lesser grades of splenomegaly. Here, however, I do not think it was diagnosed radiologically. Dr. Steiner, you did not report the spleen as enlarged?

Dr. R. E. STEINER: No, I did not mention it.

Dr. MILNE: I am afraid both the clinicians and the radiologists failed here. There is just one interesting point in relation to the spleen, and that is the Congo-red test. In our analysis of amyloid we usually find the Congo-red test is diagnostic of amyloid in the liver, this being the organ which usually contains the greatest mass of amyloid. Here of course the liver was completely clear and yet the Congo-red test was positive. I would interpret this result as having been due to the spleen, as the spleen was both large and very heavily involved, and this was probably the main site of take-up of our Congo red. I agree this does not excuse us for not making a diagnosis of splenomegaly in life.

Professor HARRISON: I think we should be careful here about using the word splenomegaly, merely because the spleen was overweight. Amyloid spleens are jolly heavy spleens.

Professor MCMICHAEL: A case of specific gravity?

Professor HARRISON: Exactly.

Dr. STEINER: We are looking for evidence of rheumatoid arthritis, but we have got no films of the hands or feet. However, the hip-joints are abnormal. There appears to be narrowing of the joint spaces due to degenerative joint disease which may have been secondary to an old burnt-out rheumatoid arthritis. So we have got evidence of a generalized joint disorder.

E.C.G. EVIDENCE OF PERICARDITIS

Dr. J. P. SHILLINGFORD: This is the problem of the raised ST segment, and in this case I think it is abnormally raised in the leads associated with the postero-lateral side of the heart, as Professor Kekwick said. There are two kinds of abnormally raised ST segment: one convex (Pardee's sign), associated with myocardial ischaemia; and the other concave, found more often in association with pericarditis. I think in this particular instance the raised ST segment suggests pericarditis. Therefore I should have strongly suspected, Professor Harrison, that there was a patch of pericarditis somewhere on the outer side of the heart and behind the left ventricle, and perhaps it may have been overlooked at necropsy.

Professor MCMICHAEL: We press our pathologists for details!

Professor HARRISON: There were loosely scattered fibrous adhesions of the pericardium but they were separable, and microscopically we found no evidence of any active pericarditis. There were adhesions but not activity.

Dr. SHILLINGFORD: From where did you take your sections? This is very important, as the electrocardiograph shows a localized disturbance.

Professor HARRISON: The normal routine sections we take are across the base of the left ventricle to include the left ventricular base anteriorly, the adjacent atrium, and the root of the mitral valve, and the like on the other side of the tricuspid; in other words, both atria, both ventricles, and the two atrio-ventricular valves. I have not got posterior base and have not got the apex of the heart.

Dr. SHILLINGFORD: This is in order because there is little evidence on the electrocardiograph that there is pericarditis on the anterior wall of the heart.

Professor MCMICHAEL: Well, I think you both win! Now, Dr. Dixon, about this rheumatoid arthritis.

Rheumatoid Arthritis

Dr. Dixon: Well, I do not think one can see at close range very much more than one can see from the auditorium. The joint space is narrowed, there is some sclerosis of surrounding bone, there is a cyst in the ileum over the right hip, and there is not much bony overgrowth of edges of the joints. There is early flattening of the top of the femoral head, particularly on the left, where one is beginning to lose ball-and-socket-type motion and get a hinge motion instead; it would do perfectly well for an old burnt-out rheumatoid. Could there have been active rheumatoid arthritis as well? We have no report of pain in the joints, but there was a high sedimentation rate. I do not know whether we have yet found any other adequate explanation for the sedimentation rate, so we cannot rule out the possibility that the arthritis was still active.

I would like to take up Dr. Milne on one point. I do not think anybody has claimed that 10% of the men in this age group have rheumatoid arthritis—not in so many words. Perhaps 10% may have some of the symptoms, such as stiffness and joint pain at some time, but rheumatoid arthritis, sufficient to take one to a doctor, occurs in about 1% of the population in this age group. Moreover, not all of these patients will get to a hospital: and even amongst those that do—mainly, of course, women with more severe disease—the number who have severe amyloid, sufficient to die of it, is probably not more than 2 or 3%.

Professor McMichael: Two or 3% of those with amyloid?

Dr. Dixon: No, 2 or 3% of those who have rheumatoid arthritis die with amyloid as the major cause.

Professor McMichael: But amyloidosis is demonstrable in about 15% or more. . . .

Dr. Dixon: Well, may be more, to a minor degree.

Professor McMichael: Well, I am very glad to have confirmation. I am not often supported against Dr. Milne's authority! Well, now, any other points on the technical details of Professor Kekwick's studies on electrolytes? I do not know whether we intended to involve him in discussion of these matters or whether we even gave him enough data.

Abnormal Biochemistry Typical

Professor E. J. King: At one point Professor Kekwick suggested that the raised serum phosphate was due to leakage of phosphates out of the cells. Now does he think that in uraemic acidosis with a lowered calcium, raised urea, and a raised phosphorus, the phosphate always comes out of the cells, or is the raised level partially due to retention?

Professor Kekwick: I am very sorry, but I don't know for certain. I think Dr. Milne woud give you a much better idea than I can, but I have assumed that it is in fact due to both, in view of the rapid fluctuations one sees in these figures.

Dr. Milne: Well, in uraemia the plasma sulphate and phosphate both increase. We usually do not burden you with sulphate estimations as we know they are technically much more difficult than phosphate. However, expressed in milliequivalents, the usual increase in sulphate is much greater than that of phosphate. This is entirely because both these ions are cleared by the kidneys. The normal clearance of sulphate is very nearly equal to the glomerular filtration rates; the normal clearance rate of phosphate is quite high, about 20 ml./min. Therefore one would expect the plasma levels of both these anions to increase if the function of the kidney was impaired, just as the blood urea does. The sulphate would be expected to increase more than the phosphate, as in fact it does. This, of course, explains the increase of the deficit between the plasma levels of sodium and chloride which is so common in uraemia. The deficit is chiefly made up by retained phosphate and sulphate. This contrasts with the acidosis of renal tubular acidosis where there is no increase in sulphate and phosphate because the glomerular filtration rate is normal, and therefore plasma chloride goes up when sodium bicarbonate goes down, giving rise to the name hyperchloraemic renal tubular acidosis in these cases. I think the abnormal biochemistry here was very typical of such an extreme case of renal failure.

Professor King: Well, in view of this, you are suggesting that the phosphate clearance has decreased—is that what I understand you to say?

Dr. Milne: The phosphate clearance in renal failure will go down as the renal failure increases. In actual fact, however—putting it mathematically—the ratio of the phosphate clearance to the urea clearance or the inulin clearance does go up. Therefore in renal failure the phosphate clearance approximates to the grossly reduced glomerular filtration rate, but in absolute values is profoundly reduced.

Professor King: Then you would think that the increased phosphates were mainly due to retention rather than leakage from cells?

Dr. Milne: That is right.

Carcinoma and Amyloidosis

Professor McMichael: One other question I would like to ask: What about the relationship of amyloid disease to carcinoma? This man had a small carcinoma, but although small it may have been there for possibly a year or two.

Professor Harrison: I do not know of any statistical association between malignant tumours in general and amyloidosis. In our own series here there has been no special incidence of tumours.

Dr. C. C. Booth: We did have a Clinicopathological Conference last Wednesday on an elderly man who died of carcinoma of his ampulla of Vater and who had what you term incidental senile amyloid of the heart.

Professor Harrison: That is correct.

Dr. Booth: And we have a Clinicopathological Conference in two weeks' time on a case with a similar association.

Professor McMichael: Amyloid is also associated with Hodgkin's disease. I just wonder.

Dr. Milne: Well, we can only date the amyloid by the duration of the proteinuria, and this would be at least one year. If Professor Harrison could say that the carcinoma could have been there for, say, possibly three or four years, I would be willing to accept this. I think that in secondary amyloid causative factors are cumulative. There is more chance of developing amyloid if the patient has two separate diseases which may be termed "amyloidogenic" than if he has a single primary cause.

Dr. Shillingford: Have we successfully explained the report on the chest *x*-rays showing that there was

moderate generalized cardiac enlargement? Is there any reason for that? He was normotensive, he had no valvular involvement, there was no amyloid of the heart. . . .

Dr. STEINER: This was an enlarged heart.

Dr. SHILLINGFORD: But we have not explained it.

Professor HARRISON: The weight was 100 g. over the normal for a man of his size, a relatively minor grade of hypertrophy.

Dr. STEINER: A point about the age of the lung tumour. These tumours can remain stationary for many, many years. We have watched them, not necessarily one year, but for four or five or even longer.

Dr. BOOTH: I wonder if there is any record of how many million cigarettes he had smoked!

SUMMING UP

Professor MCMICHAEL: While we are finding out about the cigarettes, let us ask Professor Kekwick to sum up.

Professor KEKWICK: Thank you very much. I have been most interested in this patient. There are one or two things I would very much like to endorse. Dr. Milne's statement about the complete absence of correlation between disease activity and the incidence of amyloidosis is a very important one. Some months ago Dr. Campbell Golding at my own hospital called my attention to the fact that the spleen may be tucked high up under the diaphragm and stuck there quite immobile. If such a spleen became enlarged it might not be palpable. I was delighted to hear Dr. Steiner remind us about the length of time during which carcinomas of the lung can stay in a quiescent stage. This is important when considering the effects of therapy.

Professor MCMICHAEL: We are all very grateful indeed to Professor Kekwick for submitting to this ordeal. I hope he has not found it too unpleasant. We have enjoyed his visit.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to Mr. W. Brackenbury for the photographs.

G.P. AND PREVENTIVE MEDICINE

SOCIETY FOR SOCIAL MEDICINE

[FROM A SPECIAL CORRESPONDENT]

The Society for Social Medicine at its fifth annual meeting, held last month under the chairmanship of Professor W. S. WALTON at the London School of Hygiene and Tropical Medicine, devoted its first morning to a symposium on "The General Practitioner and Preventive Medicine."

Presymptomatic Diagnosis

The subject was introduced by Professor E. M. BACKETT (University of Aberdeen), who drew attention to the well-recognized changes in the pattern of disease in this country and pointed out that these must be matched by a change in the pattern of medical care. Chronic illness accounted for more and more of the case load of the general practitioner, and all too often such disease was well established and incurable by the time it was diagnosed. That being so, effective action could be taken only if a diagnosis was reached before symptoms developed, and presymptomatic diagnosis must be classified as preventive medicine. This would, in the present state of knowledge, involve the screening of entire practices, but new equipment such as dip-sticks for urine testing, light transistor electrocardiographs, "puff meters," and fat callipers were making screening a real possibility for the interested and energetic general practitioner. The task probably would soon be made simpler by the epidemiologist as he learnt to identify the groups which were particularly prone to certain diseases.

Professor Backett went on to say that the possibility of performing such work with any degree of comprehensiveness was still something of a daydream, because suitable clinical techniques were still few. In the meantime much could be done to temper the attitude of the patient so that he became familiar with and tolerant to the preventive approach. Some general practitioners have already shown that if the patient was approached tactfully he was ready to co-operate.

Child Health

Dr. R. M. ACHESON (London School of Hygiene) said that a small but increasing number of general practitioners were taking on work in the field of child care, and that now was the time to consider the future shape of this service. Putting forward a series of recommendations for the society's consideration, he said that his first was that the interested general practitioner should be actively encouraged to undertake infant and child welfare work. One of the latter's traditional tasks was that of family adviser and friend, and how could he better establish himself as such than by seeing healthy mothers and their children at regular intervals? This was not to say that the local authority services should be curtailed unless, at some time in the future, the efforts of the G.P. should prove them to be superfluous. His second point was that general practitioners should not undertake such work without the assistance of a health visitor. To support this suggestion he gave in some detail the results of a small survey he had carried out of the use of child health and welfare clinics by mothers in three widely contrasted areas of England and Wales; he found that in those localities over 60% of all the visits to the clinics were paid by mothers with the declared intention of consulting the health visitor rather than the doctor. Thirdly, he suggested that practitioners undertaking infant and child welfare work should be properly qualified in the preventive aspects of paediatrics; the average undergraduate course was far too heavily orientated towards curative medicine and there was no suitable postgraduate training. Why not change the emphasis of the Diploma in Child Health from cure to prevention, and open a list, similar to the obstetric list, for practitioners who, holding this diploma, undertook infant welfare work in their practices? They should, of course, be paid extra for doing this.

Several of those discussing the paper were not satisfied that the conclusion that the health visitor is important was well founded. Dr. S. A. SKLAROFF (University of Edinburgh) felt that the high consultation rate ascribed to her could be a result of her being overprotective to the doctor and thus dealing with the majority of problems herself. Dr. E. G. KNOX (University of Durham) questioned the value of her advice in terms of the health of the community she cared for, and Dr. J. A. D. ANDERSON (Edinburgh) wondered whether the mothers' preference for the health visitor's advice could be explained by the fact that they knew her better than the doctor. Replying, Dr. ACHESON felt that the health visitor was pivotal to local authority services and that there was abundant evidence for the efficiency of these over recent decades; this in itself was a reason why she should take some of the weight off the general practitioner's shoulders. Dr. JEAN MACKINTOSH (University of Birmingham) agreed, and pointed out that the training of the health visitor was continually improving and that she really was becoming an expert in child development. Speaking as general practitioners, Dr. W. N. PICKLES (Aysgarth) mentioned the place the general practitioner had in the routine examination of the newborn, and Dr. JOHN WOODALL (St. Paul's Cray) said that a general practitioner by taking on infant and child health work in his practice ensured that

mothers obtained consistent advice because it came from one person, but added that in some areas poor liaison existed between G.P.s and health visitors.

Mental Health

Mr. S. P. W. CHAVE (London School of Hygiene) introduced the subject of the general practitioner and mental health by referring to survey work he had carried out on the care of mental illness in general practice. He had found that in a defined population of many thousands, cared for by several G.P.s, only one adult complained of symptoms of mental ill-health in a given year for every two who had no such symptoms. It ranked tenth when all diseases were listed according to the main groups of the international classification. By far the commonest diagnosis was neurosis, and the G.P. himself seemed to be capable of dealing with such cases. In men this complaint was most often associated with difficulties experienced at work, and in women with worries about the home and children. One interesting feature of the survey was the difference in the frequency with which the practitioners diagnosed mental ill-health; Mr. Chave believed that this was in part due to the selection of a general practitioner by patients, and in part to the differing diagnostic techniques of the doctors. From the point of view of prevention all the G.P. could hope to do for the psychoses was to make an early diagnosis, as Professor Backett has suggested, at a stage when the disease was treatable. Much could be done, however, in aftercare of patients discharged from mental hospitals and in marriage and family guidance.

Professor R. S. F. SCHILLING (London School of Hygiene) asked how the pattern of mental illness in an area where the population had all been rehoused compared with that in a better-established area; Mr. CHAVE replied that the hospital admission rates for mental disease in a new town community were lower than those elsewhere. In answer to a question from Dr. R. I. MCCALLUM (University of Durham), he added that the original fears that populations of new towns would always have a grossly atypical age-structure were not being realized.

Occupational Health

Lord TAYLOR (Harlow Industrial Medical Service) was the last speaker from the platform, and he put forward cogent arguments for occupational health services being run by general practitioners. He likened the position of the whole-time industrial medical officer to that of a doctor in the armed Services—a man who is outside the main stream of medicine; furthermore, in order to serve his employer he had to identify himself with productivity. This was not the case when a general practitioner undertook industrial medicine, for not only was he completely associated with the medical world through his practice but also, because the chief part of his income came from sources beyond the control of the management, he could act impartially in the interests of employee and employer alike. Moreover, his services were less costly to industry than those of the whole-time medical officer. Much of the work of a doctor in industry was identical to general practice, for most illness occurring at work had nothing to do with occupation; it was by chance that it happened at the work-place. Routine medical examinations were perhaps unfamiliar to the G.P.; these should be purposeful and could be made easier by the use of screening questions. Lord Taylor finished by describing the requisites of a general practitioner in industry as medical capability, common sense, and disciplined curiosity.

Dr. R. E. W. FISHER (London), speaking from 15 years' experience of industrial medicine, said that he did not believe a whole-time medical officer need identify himself with productivity; his job was quite simply to look after the people who were at work in his industry. Professor A. MAIR (University of St. Andrews) raised two points: first he believed that Lord Taylor had oversimplified the problems facing the general practitioner in industry, and secondly he thought that regular refresher courses would be necessary—perhaps three months in every four years. Lord TAYLOR agreed that refresher courses had an important place in this field, but felt that a three-months course would be far too long.

FIFTH WORLD ASSEMBLY OF THE ISRAEL MEDICAL ASSOCIATION

[FROM A SPECIAL CORRESPONDENT]

The Israel Medical Association held its Fifth World Assembly in Jerusalem from August 12 to 26 under the chairmanship of Professor J. LANDAU. The Israel Medical Association was founded in 1911, and this jubilee meeting was attended by both the Prime Minister of Israel, Mr. D. BEN GURION, and the Minister of Health. Britain was represented by Dr. E. E. LIEBER.

Professor Zondek's Address

The scientific proceedings were opened by Professor HERMANN ZONDEK, head of the scientific medical council of the I.M.A. The subject of his address was the unsolved mystery of the cell, which, he said, had intrigued biologists for decades. He spoke of the specific rhythm inherent in cellular activity, the sense of time (Portmann spoke of a clock built into the cytoplasm), the gift of orientation as possessed by birds (the capacity of certain cell aggregates within the small brain to steer their world-wide flights), the gift of self-regulation proceeding interminably in the same direction and indefinitely producing the same forms. What might this "self" be? It could not be the ego, as all these cell-phenomena proceeded in the sphere of the unconscious mind. This problem led one straight to the core of the life problem, and he doubted whether the exact sciences would ever be able to find an answer to it. The conception of an organizing power, "a subconscious consciousness," which seemed to arrange and supervise the processes of life in an orderly manner, would remain valid.

Professor Zondek said that in cell research we had begun to study and dimly to understand the function of the cell nuclei, carrying, among others, the mysterious laws of heredity, and the cytoplasm with its independent units such as microsomes, microbodies, and mitochondria endowed with specific functions. Apart from the finely attuned nervous and chemo-hormonal regulatory system, originating in the hypothalamus and the pituitary gland, the cell also possessed autonomous regulative forces, which applied not only to the cell as a whole but to the subcellular particles, as he had observed in the thyroids of cretins. During the past forty years he had been thinking in terms of "cellular endocrinology." Now we had reached the stage when we were entitled to speak of a "subcellular endocrinology" which might open up a wide range of new theoretical and practical aspects. Hormonal regulation extended not only to all vegetative functions such as growth, metabolism, reproduction, and circulation, but also to psychical functions, as evidenced by disturbances of mental balance during puberty, the depressive states associated with the puerperium and the climacterium, the occurrence of genuine psychoses (schizophrenia) after steroid administration, the mental retardation resulting from congenital thyroid deficiency, and the myxoedema psychosis relieved by thyroid therapy. He postulated that since the brain cells were particularly rich in enzymes we might deduce that the hormonally induced alterations in the cortical cells were brought about in the same manner both physiologically and pathologically as in other body cells.

Scientific Programme

There were a large number of scientific contributions on such subjects as genetic factors in haemolysis, atherosclerosis

in different ethnic groups, tropical disease, poliomyelitis, rheumatic fever, leprosy, psychological medicine, and public health. It is possible here to summarize only a few of the papers.

Dr. S. SYMAN, director-general of the Israel Ministry of Health, speaking on international health, referred to the urgent needs created by the emergence of new States, particularly in Asia and Africa. Israel had effectively joined the efforts of W.H.O. and these new and developing countries. There were a school of nursing in Burma and a team at the Singapore Medical School. Other Israeli health officers were serving in the Belgian Congo, Ghana, Liberia, and so on. The Hadassah Medical School was about to start a medical course for students from Africa and Asia.

Dr. A. M. COHEN (Israel) spoke on the effect of environmental changes on the prevalence of diabetes among different ethnic groups in Israel. It had been found that the prevalence of diabetes among the Ashkenazi and Sephardi groups did not differ from that of non-Jewish communities in other parts of the world. On the other hand, the prevalence of diabetes among the Yemenite group, which formed a specific ethnic group, was extremely low among the newcomers, but in the case of the older settlers approximated to the incidence among the Ashkenazi and Sephardi groups.

Dr. F. DREYFUSS (Israel) had made some clinical and epidemiological observations on coronary heart disease and hypertension. The low incidence of myocardial infarction among Oriental Jews in the country had provoked interest in studies of the incidence and character of coronary heart disease among the various communities in Israel. A group of Jews from Cochin (India) had been investigated. Neither coronary disease nor hypertension seemed to be frequent. Their fat intake, mostly from vegetable sources, was about 60 g. per day. No clear-cut example of myocardial infarction had been discovered. The results of a joint investigation of an Arab village population showed a low blood-cholesterol level. No case of myocardial infarction had been discovered, and altogether the incidence of coronary heart disease seemed to be low.

Dr. E. E. LIEBER (Britain) gave a paper on medical aspects of the chemical industry. It was the task of the medical officer in a chemical factory, he said, to put right conditions which exposed the worker to toxic materials, and in order to do this he must be familiar with methods of determining concentrations of toxic vapours and fumes and dusts, and understand something of sampling and quantitative analysis.

While in general practice the main purpose of medical examination was to diagnose and treat the disease, in industry it was primarily preventive, and it followed, therefore, that it must always have regard to the particular conditions of the individual's employment.

Dr. EGON PLESCH (Britain) discussed the theoretical aspects of the psychogenesis of rosacea and allied reddening disorders. In twenty cases he had found that all patients were suffering from conspicuous paranoid trends. The mothers of the patients were themselves suffering from severe emotional disturbances. He discussed the mechanism of paranoid transformations in the child under the influence of deprivation of maternal affection, and the transmission of the mother's anxiety to the infant.

Dr. L. MILLER (Israel) spoke on problems of mental health in Israel. Psychiatric and preventive mental health services had been established on a regional basis, he said. These services were to a large extent meeting the most urgent curative needs. The hospital services in each region were varied according to the patient's needs, and were "open" and community-orientated. As everywhere, the major deficiencies were in the early diagnosis and care of the patient while still at home, and in his rehabilitation and follow-up after hospitalization. The most urgent mental health problems in Israel to-day were, however, related to the process of social and cultural change which the hundreds of thousands of immigrants from Islamic countries were now undergoing in Israel.

MEDICAL SCHOOL OPENINGS

CHARING CROSS HOSPITAL

At the Opening Day Ceremony and Prize-giving at Charing Cross Hospital Medical School on October 12 the DUCHESS OF DEVONSHIRE deputized for her husband, whom, she explained, had been sent to Canada on Government business. They were in a strange position, she said. She had looked through the ranks of distinguished persons who had made this inaugural address over many years past, and had found that they had all been men—and all of them most dangerously clever ones. "To-day, however, you are faced with a woman who has never passed an examination in her life."

Selection of Students

The Duchess went on to speak about the selection of university students. The highly personal nature of the relationship between doctor and patient must always be borne in mind when considering potential students for admission to medical schools. Personality and temperament went hand in hand with academic ability.

In his annual report, the dean, Professor W. J. HAMILTON, also discussed the selection of students. It was becoming an ever-increasing problem to find places for all students considered suitable for places in a university, he said. There had been much discussion about a scheme for setting up a clearing-house through which all students who wished to enter a university would apply. "The deans of the London medical schools were unanimously against such a clearing-house for the admission of students to the medical schools in London," said Professor Hamilton. They had felt that every student should have the opportunity of applying directly to the medical schools of his choice; and it was only fair to say that most students applied to more than one school, and many to all. This, of course, involved a great deal of work for selection committees, but they thought the labour worth while. "We all have fairly definite ideas of the type of individual we would like to recruit into medicine," said Professor Hamilton. "He should be a presentable and understanding person of good mental and physical ability, with an unforced and friendly approach to people, humanitarian in his ideals, and of stable character."

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Vitamin A

Chemistry.—Vitamin A is a complex primary alcohol synthesized in the wall of the small bowel from carotene present in foods. Green vegetables, carrots, egg yolk, milk, and butter are common sources of carotene. Vitamin A itself is present in liver and fish-liver oil. It is often added to margarine and milk powders. Standardization is by biological assay in rats. An international unit is the activity of 0.3 μg. of vitamin-A alcohol. Vitamin A is heat-stable but is destroyed by light and oxidizing agents.

Pharmacology.—Vitamin A is necessary for the formation of the visual purple of the retina and for the maintenance of epithelial tissues in a healthy condition. Gross deficiency causes night blindness, xerophthalmia, hyperkeratosis ("toad skin"), and makes the patient susceptible to the formation of renal calculi. Adults need 2,500 to 5,000 i.u. daily and up to 50% more during pregnancy and lactation.

Preparations.—Concentrated vitamin-A solution contains 50,000 i.u. per g. Vitamin-A capsules (strong) *B.N.F.*

contain 50,000 i.u. each. Halibut-liver-oil capsules contain 4,500 i.u. each with some vitamin D. There are numerous proprietary preparations.

Toxic Effects.—The smallest regular dose recorded as producing chronic toxic effects is 50,000 i.u. daily for 18 months.[1] Signs and symptoms are varied and not very specific. The commonest are fatigue, pains in bones and joints, loss of hair, and desquamation and fissuring of the lips; mild anorexia and loss of weight have also been reported. The liver and spleen may be enlarged. Tests of liver function remain normal. Withdrawal of vitamin A gives prompt relief. More acute symptoms have sometimes followed a single large dose (300,000 i.u.), especially in babies suffering from hydrocephalus with increased production of cerebrospinal fluid. It is interesting to note that the liver of the polar bear is known to Arctic peoples to be toxic. It contains up to 18,000 i.u. per g.[1]

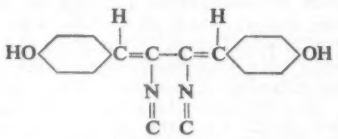
REFERENCE

[1] Stimson, W. H., *New Engl. J. Med.*, 1961, **265**, 369.

Xanthocillin

"Zynocin" lozenges and "zynotracin" ointment (Distillers Company (Biochemicals)).

Chemistry.—Xanthocillin, which is isolated from a strain of *Penicillium notatum*, is a yellow crystalline substance with two components, xanthocillin X and Y in the proportions 4:1. They are chemically very similar, and both are therapeutically active. Xanthocillin X has the probable formula:



Bacteriology.—This antibiotic has a wide antibacterial spectrum, being active *in vitro* against most pathogenic Gram-positive and Gram-negative organisms, including *Proteus vulgaris, Ps. pyocyaneus,* and *E. coli.* It has a limited activity against some streptococci. It is said to be active against the tubercle bacillus, fungi, and yeasts. Acquired resistance and cross-resistance have not been reported.

Pharmacology.—A relatively high toxicity and low solubility make it unlikely that xanthocillin will be administered systemically. It is used as a topical antibiotic—a 0.45% ointment for skin and mucous membranes and 1-mg. lozenges. Both formulations at present available include other ingredients than xanthocillin. Zynotracin ointment also contains zinc bacitracin (500 units per g.) and hydrocortisone (1%). The lozenges also contain benzocaine (5 mg.).

Therapy.—Xanthocillin cream is not available without the addition of hydrocortisone, and hence zynotracin ointment should not be prescribed for the treatment of ordinary skin infections such as impetigo, folliculitis, or boils. In any case there is no evidence that xanthocillin is superior to other antibiotics for these conditions. Zinc bacitracin is incorporated in zynotracin for its anti-streptococcal activity, and the hydrocortisone for its suppressive effect on eczema or dermatitis. Hence the principal indication for its use would be an infected eczema or dermatitis. The proportionate role of secondary infection and eczematous inflammation are frequently difficult to assess in such cases, but zynotracin is likely to be as useful as other antibiotic–topical-steroid combinations. Twice- or thrice-daily applications should be adequate.

Side-effects.—Xanthocillin has not yet been used extensively. Allergic sensitization has been reported. There is no evidence of allergic cross-sensitivity to other agents nor of bacterial resistance or cross-resistance.

N.H.S. Basic Price.—Zynocin lozenges, 12 for 2s. 6d.; zynotracin ointment, 5-g. tube for 5s. 6d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Record of Antitetanus Immunization

SIR,—Professor William Gissane in his letter (October 14, p. 1020) has drawn attention to a daily question posed to every casualty officer. What is the state of immunity of a wounded child needing protection against tetanus? It is unlikely that obligatory immunization would much simplify the situation, as is evidenced by the experience gained in the practice of vaccination. This was compulsory until 1948, but more than half of the children remained unprotected. A better result can be obtained with good publicity. It was stated this week that 85% of the toddlers in Hull have been immunized against poliomyelitis.

In Cumberland we have given this matter anxious thought, and we are about to introduce what we hope is a new approach to this issue. We try to ascertain the state of immunity by reference to three sources. Firstly, we appeal to the parental memory, but this is notoriously fickle, particularly when a patient is one of a large family. Secondly, we send a questionary to all practitioners in our area. We ask them if they use the triple antigen and if so at what date they adopted it. From this datum a list was compiled which can be consulted for a given child. Thirdly, we have started, with the whole-hearted co-operation of the county medical officer, the assemblage of an inoculation card-index. The public health doctors supply the hospital with details of all children they have protected with toxoid.

We appreciate that geographically we have an isolated population and that our patients have practically no choice of hospital. For these reasons our scheme would probably not work in an urbanized area.—I am, etc.,

Whitehaven, Cumberland. J. P. TURNEY.

SIR,—Professor William Gissane, as others have done before, advocates tattooing as a personal record of tetanus immunization (October 14, p. 1020). Even if this were acceptable to parents, which I do not believe, it would be of no use unless the dates toxoid had been given were recorded. I have suggested[1] that the best way of making the necessary information available in the hospitals is for the appropriate local health authority (or authorities) to make available, and keep up to date, in the main casualty centre for the area, an alphabetic card-index of all persons known to the authority (authorities) to have been immunized against tetanus, with the relevant dates. Such an idea would be practically comprehensive in respect of immunized children. It could be consulted at any time, day or night, and by any hospital in the area (by telephone). This method, suggested to me by one of my staff, Mr. W. Stamp, would, I believe, be a great improvement on any now practised.

Professor Gissane also hopes for obligatory immunization: that went out in 1948—it is very unlikely to return.—I am, etc.,

Health Department, Exeter, Devon. E. D. IRVINE.

REFERENCE

[1] Irvine, E. D., *Med. Offr*, 1961, **106**, 201.

in the COLD WAR

against respiratory congestion

'Actifed'

Tablets
Containing 2.5 mgm. triprolidine hydrochloride ('Actidil') and 60 mgm. pseudoephedrine hydrochloride in each tablet.

Syrup
Containing 0.88 mgm. triprolidine hydrochloride ('Actidil') and 21.3 mgm. pseudoephedrine hydrochloride in each fl. drachm of syrup base.

'Actifed' Tablets and Syrup

Given ORALLY, 'Actifed' Tablets bring safe, rapid and prolonged relief without risk of secondary engorgement or inhibition of ciliary activity. 'Actifed' Syrup is now also available. A safe, palatable alternative to the tablets, it is especially suitable for children.

'Actifed' Tablets or Syrup is taken 2 or 3 times a day, the dosage being 1 tablet for adults and children over 12 years; ½ tablet or 1 teaspoonful of syrup for children 2 to 12 years; ¼ to 1 teaspoonful of syrup for infants.

against cough

Compound Linctus
Containing 1 mgm. triprolidine hydrochloride ('Actidil'), 20 mgm. pseudoephedrine hydrochloride and 7.5 mgm. codeine phosphate in each fl. drachm of syrup base.

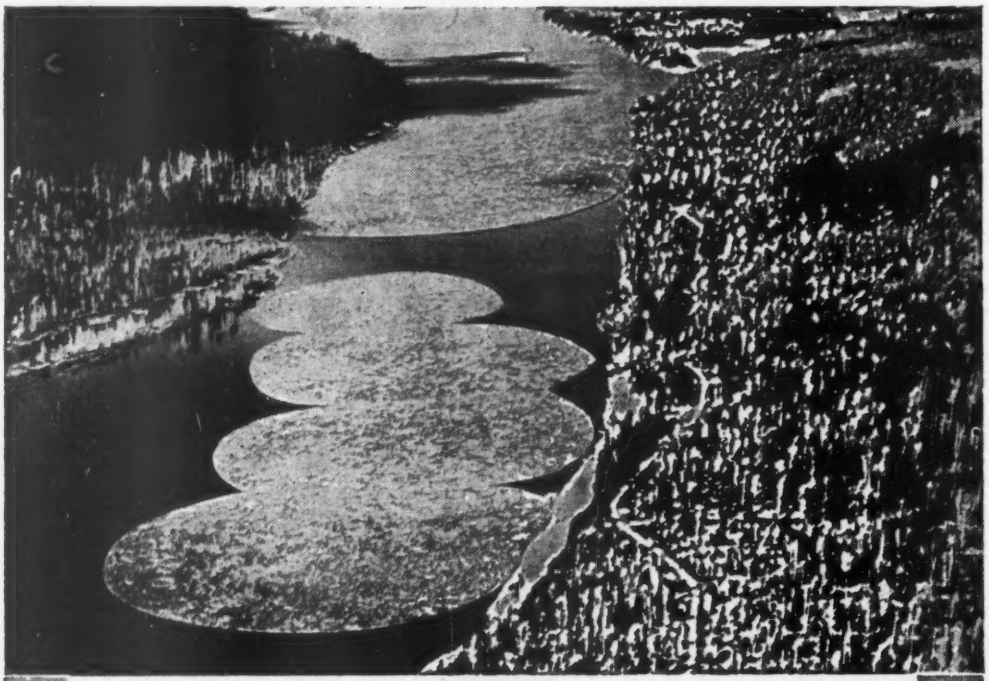
'Actifed' Compound Linctus

A pleasantly flavoured Linctus; combines the properties of 'Actifed' with the cough suppressant action of codeine phosphate; particularly useful if the cough is associated with respiratory congestion, e.g. in the common cold or in bronchial asthma.

'Actifed' Linctus is taken every 4 to 6 hours; 1 to 2 teaspoonfuls for adults, ½ a teaspoonful for children of 2 to 12 years.

'Actifed'

BURROUGHS WELLCOME & CO (The Wellcome Foundation Ltd) LONDON



Circular booms or "sacks" each consisting of about 25,000 logs, on the Gatineau River, Quebec, one of Canada's richest sources of pulp wood. (Photograph by courtesy of the National Film Board of Canada.)

—but when blood vessels are occluded...

ANTICOAGULANT THERAPY

with

*PULARIN

(heparin-Evans)

available in 5 ml. rubber capped bottles containing 1000 I.U., 5000 I.U., and 25,000 I.U. per ml. and as a G.P. Emergency Pack of 12,500 I.U. in a 1 ml. ampoule.

and *DINDEVAN

(phenindione-Evans)

available as tablets of 10 mg. in containers of 100 and 500 and as scored tablets of 50 mg. in containers of 25, 100, and 1000.

or *MAREVAN

(warfarin sodium-Evans)

available as scored tablets of 3 mg. in containers of 100 and 1000 and as scored tablets of 5 mg. in containers of 25, 100 and 250.

A copy of the brochure 'Essentials of Anticoagulant Therapy' will be sent by Medical Information Department on request

*Trade Marks

EVANS MEDICAL

EVANS MEDICAL LTD

LIVERPOOL and LONDON

700

Milk Proteins in Ulcerative Colitis

SIR,—The paper by Drs. K. B. Taylor and S. C. Truelove (October 7, p. 924) on the role of milk protein in ulcerative colitis may make the following case of interest.

A male infant was born normally at term, weighing 6 lb. 2 oz. (2.78 kg.); there is one healthy sibling. Moderate tenesmus and colic were noticed from the ninth day, but the stools were normal. In the seventh week, two days' diarrhoea with increase in the colic and tenesmus led to admission on July 11, 1961; blood and mucus had been passed during the preceding 12 hours. The faeces contained blood and mucus in moderate amounts for two days and the diarrhoea ceased after five days, treatment being oral sulphonamide and streptomycin, with glucose/electrolyte solution initially. Two faecal cultures were negative for the usual pathogens, *Staph. pyogenes* being cultured in the third. Feeding since birth had been with a dried-milk product, this being changed to another dried milk in hospital, at first half-cream, then full cream.

Proctoscopy on the eighth day showed a moderate proctitis, the examination producing some blood and mucus. On the thirteenth day diarrhoea with blood and mucus recurred, treatment being with glucose/electrolyte solution and chloramphenicol. Half-cream dried milk feeds were resumed but some mucoid diarrhoea and tenesmus persisted. Barium enema (Dr. J. Gately) on the twenty-first day was considered typical of ulcerative colitis with loss of haustration as far as the splenic flexure, and hyperirritability; proctoscopy still showed an inflamed mucosa. From the twenty-second day milk feeds were replaced by a soya-bean liquid food ("sobee," Mead Johnson) with general improvement, weight gain being 29 oz. (822 g.) in 18 days, as compared with 5½ oz. (156 g.) in the previous 22 days. The tenesmus gradually lessened; proctoscopy on the thirty-fourth day showed only slight mucosal inflammation. The infant has since remained well.

It seems reasonable to infer that this infant suffered from moderate ulcerative colitis attributable to cow's milk allergy, although it remains to be seen whether exclusion of milk from the diet will lead to permanent arrest of the disease. In the last five years I have seen two clear-cut instances of cow's milk allergy and at present have two other infants under my care whose symptoms were probably of similar causation; none of these infants appeared to have ulcerative colitis, though all had severe diarrhoea which persisted until milk was replaced by soya-bean feeds. Two of these infants, seen some years ago, were able to tolerate moderate amounts of cow's milk following its cautious introduction to the diet over several months. Simple patch tests with cow's milk in the infant reported did not show any skin sensitivity. It will be interesting to search for blood-borne antibodies to milk in this infant, and in other instances of suspected milk allergy, by the interesting methods reported by Drs. Taylor and Truelove.—I am, etc.,

Regional Hospital, Galway. B. MCNICHOLL.

Liver Perfusion

SIR,—The preliminary communication by Mr. A. Eley on liver perfusion (September 23, p. 806) deserves comment because, as he states, it will be of interest to other workers in this field.

Perfusion of the human liver presents a technical challenge so complex that most workers have been content to sacrifice complete isolation for simplicity. Thus Aust and Ausman[1] have cross-clamped the abdominal aorta below the coeliac axis and used simple cannulation of the vena cava via the saphenous vein to collect hepatic venous outflow; they have perfused five patients this way, via the portal vein, and mention their method for using hepatic artery inflow. We have developed a similar technique with the addition of regional hypothermia for visceral and spinal-cord protection, thus allowing clamping of both vena cava and aorta above the diaphragm, but now regard liver perfusion as unjustifiable in human malignant disease at the present time.

The drugs available and suitable for use by perfusion have a minimal action against adenocarcinoma, while those known to be most effective in gastrointestinal carcinoma seem to be more effective when given over a prolonged period of time. At present no form of chemotherapy for patients with hepatic metastases can be regarded as curative, and few such patients have symptoms so severe as to justify the major surgery involving extensive thoracic and abdominal approaches which Mr. Eley describes. Should the liver be diffusely involved with growth, its very size and rigidity may well make the operation hazardous, if not impossible.

It seems to us that if palliative or life-prolonging chemotherapy is to be used at all, it will be best applied in those patients whose hepatic secondaries are discovered at the operation for removal of the primary lesion. Treatment should then be administered by a method involving minimal additional surgery at this operation. For these reasons, we feel that intra-arterial infusions of anticancer agents have more to offer; catheters can easily and accurately be placed at any abdominal operation (or percutaneously without operation), and the drugs can be given over a period of days or weeks thereafter. The whole range of antimetabolites can be used by this technique, whereas because of their slow mode of action they would seem to be ineffective in a perfusion.

Although it remains to be shown which method is the more effective, we would urge Mr. Eley, and other workers in this field, to consider the relatively simple alternative of intra-arterial infusion before using an ingenious method which might produce an effect on "hepatic metastases in humans," but which is certainly difficult to justify in treating men and women suffering from advanced malignant disease.—We are, etc.,

Department of Surgery, Bristol Royal Infirmary, Bristol 2

H. J. ESPINER.
K. D. J. VOWLES.

REFERENCE

[1] Aust, J. B., and Ausman, R. K., *Cancer Chemotherapy Report*, 1960, **10**, 89.

Spironolactone and Potassium Output

SIR,—Dr. E. J. Ross has pointed out (May 27, p. 1508) that an aldosterone antagonist does not abolish the potassium diuresis caused by a benzothiodiazine diuretic such as chlorothiazide. We present our findings here from an advanced case of cirrhosis which we studied over seven weeks.

An 80-year-old man with cirrhosis was admitted for the fifth time to hospital because of increasing ascites. He was excreting 31 mEq of sodium and 27 mEq of potassium in the urine per 24 hours; the serum sodium was 141 mEq/100 ml. and the serum potassium was 3.6 mEq/100 ml. He had been having 800 mg. of a spironolactone ("aldactone") four times weekly, mersalyl three times weekly, and potassium chloride daily. Initial paracentesis was a failure as he developed a low sodium state (serum sodium 127

mEq/100 ml.), with hypotension; the urinary sodium excretion fell to 1 mEq per 24 hours; and the ascites reaccumulated within a week.

He was given a low sodium diet, and had two trial periods of three days on a regimen of 400 mg. of spironolactone daily, 2 g. daily of chlorothiazide on the second and third days, and a mannitol infusion on the second day.[1] The sodium output increased on the second and third days, and the potassium output increased in the first period, and fell during the second period, as shown on the chart.

During a third period of a week, when potassium chloride was also given, the initial diuresis only lasted four days. The dose of spironolactone was doubled, and a dramatic increase in both sodium and potassium output occurred. This continued for two weeks, but dropped when the dose of spironolactone was lowered and rose when it was again increased. After six weeks the patient had lost over 1½ stones (9.6 kg.) in weight and was fit to be discharged home.

This study supports the conclusions that spironolactone, while facilitating an increased excretion of sodium by the action of chlorothiazide, does not necessarily prevent a concurrent increase in potassium output in the urine. Although part of the increased potassium output might have initially been due to the administered potassium chloride, the quantity of potassium excreted thereafter followed closely that of the sodium. That the striking increase in sodium output was due to the increased dose of spironolactone is shown by the variation in urinary excretion of sodium occurring simultaneously with the change in the dose of spironolactone in the last two weeks, when the dose of chlorothiazide was constant.

We support Dr. Ross's conclusion that potassium supplements should be given to cirrhotics treated with combinations of spironolactone and benzothiodiazine diuretics. Spironolactone itself may not prevent excessive loss of potassium in the urine, and as this may aggravate hepatic failure potassium salts should be given by mouth. Dr. Ross draws attention to the increased sodium excretion following the administration of potassium supplements. This has been shown to occur physiologically in normal subjects to whom a large dose of a potassium salt has been given.[2] Perhaps this is due to inhibition of the action of aldosterone by the increase of total body potassium.—We are, etc.,

St. Pancras Hospital (U.C.H.),
Geriatric Unit,
London N.W.1.

ARNOLD J. ROSIN.
DAVID HATCH.

REFERENCES

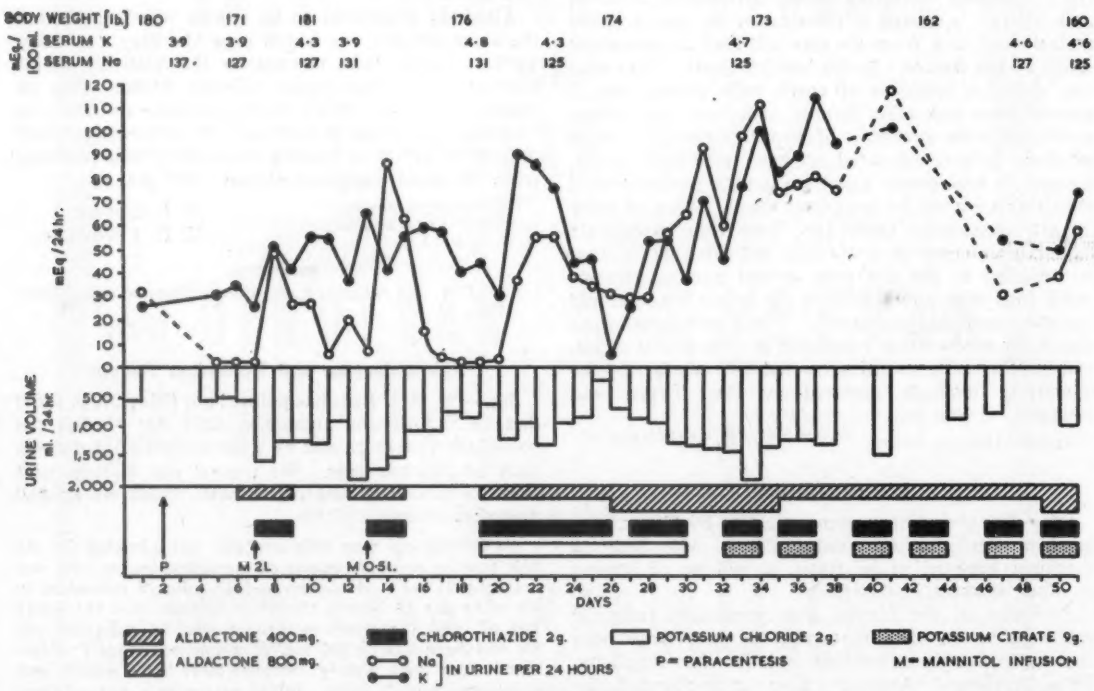
[1] Shaldon, S., McLaren, J. R., and Sherlock, S., *Lancet*, 1960, 1, 609.

[2] Gamble, J. L., *Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid*, 1954, 6th edition. Harvard University Press, Cambridge, Mass.

Steroids in Systemic Lupus Erythematosus

SIR,—The article by the Collagen Diseases and Hypersensitivity Panel on the treatment of systemic lupus erythematosus with steroids (October 7, p. 915) has been culled from a sufficiently large number of cases to provide an excellent basis for assessment in such a protean disease. It is stated that "in a lethal disease that is subject to spontaneous remissions . . . the value of any therapeutic agent is difficult to assess." The panel reaches the conclusion that renal involvement and leucopenia indicate a poor prognosis and that a uniformly bad prognosis is expected in cases treated by methods other than steroids and hence "at the present time steroids should be used in all patients severely ill with S.L.E."

The following case report is of interest because the details and history illustrate an opposite view and thus the difficulties of dogmatizing.


BODY WEIGHT (lb.) 180 171 181 176 174 173 162 160
mEq/100 ml. SERUM K 3·9 3·9 4·3 3·9 4·8 4·3 4·7 4·6 4·6
SERUM Na 137· 127 127 131 131 125 125 127 125
mEq/24 hr.
URINE VOLUME ml./24 hr.
P
M 2L
M 0·5L
DAYS
ALDACTONE 400mg.
ALDACTONE 800mg.
CHLOROTHIAZIDE 2g.
POTASSIUM CHLORIDE 2g.
POTASSIUM CITRATE 9g.
Na K IN URINE PER 24 HOURS
P= PARACENTESIS
M= MANNITOL INFUSION

Daily urine volume, and sodium and potassium output, during the administration of spironolactone and chlorothiazide.

A housewife, then aged 48 years, was investigated in August, 1951, at a cottage hospital for polyarthritis. Associated raised E.S.R., leucopenia, proteinuria, rash, and prolonged swinging fever suggested a diagnosis of S.L.E. She was transferred to another hospital for more detailed investigation. No L.E.-cell phenomenon was found and a final diagnosis five months after onset was rheumatoid arthritis with a urinary tract infection. Treatment with chloramphenicol, phenylbutazone, and analgesics was recommended.

For the next eight months she followed an up-and-down course characterized by arthritis, tachycardia, fever, and a raised E.S.R. which ended in her readmission. After two months, during which no L.E.-cell phenomenon was discovered, she was again discharged with the diagnosis of rheumatoid arthritis and treatment with mepacrine, 300 mg. daily, had been instituted. This treatment was popular about that time. Response was swift and maintained. Six months later (July, 1953) she had no arthritis, was much increased in weight, and had no subjective complaints. The raised E.S.R., proteinuria, and leucopenia remained substantially unchanged. In September, 1953, mepacrine was discontinued. During the intervening years she has been seen regularly and has kept very well. Proteinuria had been noticed to persist throughout but no other tests were followed.

In March, 1961, she relapsed with polyarthritis, fever, and raised E.S.R. As an out-patient her blood was examined for the L.E.-cell phenomenon and found positive on the first test. Admission confirmed this finding. Treatment with hydroxychloroquine sulphate ("plaquenil sulphate"), 200 mg. thrice daily, produced a rapid remission of symptoms, and at the date of writing (October, 1961) she remains subjectively well and is continuing with chloroquine in reduced dosage.

When first she reported over ten years ago she was seriously ill and looked at one time as though she were going to die. The response then to the antimalarial drug mepacrine, prescribed for a presumed rheumatoid arthritis, was dramatic. A complete remission lasted for over six years. The relapse this year presented little difficulty in diagnosis and has responded just as satisfactorily to the other antimalarial drug chloroquine. Steroids have not been required so far.—I am, etc.,

Wallasey. C. H. STEWART-HESS.

Safety of Canned Foods

SIR,—I have read with interest your leading article (August 5, p. 362) with respect to the possible hazards of the "metal content" of canned foods. About the turn of the century there was considerable interest in the safety of such foods, particularly with reference to tin. This concern, although it lasted well into the 1920s, gradually waned.

In reviewing the literature, one is unable to find truly adequate evaluations not of possible acute hazards, the primary concern of the period, but rather of the possibility of chronic, particularly subclinical, effects. Admittedly toxicology, biochemistry, and their related disciplines have come a long way since, but nevertheless investigations which would now be considered adequate do not appear to have been performed, particularly with respect to tin. This is emphasized by the fact that it was not known until 1958 that inorganic tin given to experimental animals by an appropriate route and in appropriate dose would produce the classical lower-nephron lesions of heavy-metal poisoning. In that year it was reported that rats injected intraperitoneally with relatively large amounts of tin in the suspension prepared by adding $SnCl_2.2H_2O$ to distilled water invariably developed such lesions.[1]

Although it is generally stated, as may well be the case, that the amount of tin in canned foods is of negligible importance and that only very small amounts of it are absorbed, there is a suggestion in the literature that the amount absorbed increases with prolonged exposure, a point which is among the many apparently not yet adequately evaluated. In addition, tin is regularly reported in trace-metal analyses of human tissues, which indicates that it is absorbed at least to some extent. In view of the lack of specific information which undoubtedly contributed to the uncertainties of the debate in the House of Lords to which you refer in your leading article, everyone should heartily endorse your plea for further research and continuous review as our knowledge in the pertinent collateral fields continues to expand.—I am, etc.,

WILLIAM HADDON.

State of New York Department of Health, U.S.A.

REFERENCE

[1] Haddon, W., jun., *Annual Report of the Division of Laboratories and Research, New York State Department of Health*, 1958, p. 41.

Diuretics and the Eye

SIR,—May I raise two points in Dr. Dorothy A. Campbell's lecture on diuretics and the eye (August 19, p. 467)? (1) In the discussion Dr. Campbell argues that biochemical changes in the blood may affect intraocular pressure in the glaucomatous eye, though there is little effect in the normal eye, because of impaired outflow in the former. But earlier she writes that wide-angle eyes were alone studied, in order to eliminate pathological obstruction to aqueous outflow. (2) Later in the discussion she seems to suggest that diuretics act by lowering blood sodium and osmolarity. Would not lowering the osmolarity be expected to increase water inflow and tend to raise intraocular pressure? Indeed, urea is said to lower intraocular pressure through a rise in osmolarity.

I am not very buoyant in biochemical waters, and would be grateful for some clarification.—I am, etc.,

Kirkby, Liverpool. H. M. ROSE.

*** We showed Dr. Rose's letter to Dr. Campbell, who replies below.—ED., *B.M.J.*

SIR,—I am grateful to Dr. H. M. Rose for pointing out certain discrepancies in my discussion on the mode of action of diuretics on the eye. Where several factors may be at work it is difficult to elucidate the action of any one of them.

Mechanical obstruction of the angle of the anterior chamber was originally regarded as the primary factor causing glaucoma. It certainly plays a part in causing an impaired outflow of aqueous and sustaining a basic increase of intraocular pressure. Recent evidence has shown, however, that the effect is, in fact, static rather than dynamic. For instance, the *rate* of outflow of aqueous does not change in the water-drinking test[1] nor after acetazolamide.[2] My mention of the possible effect of an impaired outflow was made with reference to the water-drinking test, which depends on the two factors of impaired outflow and of haemodilution. The effect of the former would be reduced to a minimum in the wide-angle eye, and in this case the dilution of the blood and the fall in osmolarity becomes the dominating factor. In fact, the changes in intraocular pressure in the water-drinking test have been shown to vary with the state of haemodilution.[3]

With regard to Dr. Rose's second point, two factors are concerned: (1) the change in osmolarity of the blood and (2) an alteration in the electrolyte balance. When both are affected concurrently (as after the action of acetazolamide and methazolamide) it is impossible to say in the present state of our knowledge which has the more significant action. When, however, the main change occurs in osmolarity of the blood (as after urea or water), the effect on intraocular pressure can obviously be explained in those terms. In the case of aminometradine or chlorothiazide neither factor seems to be disturbed, with the net result that there is little or no effect on intraocular pressure. It is noteworthy that, although these two diuretics vary in the amount of diuresis which they promote, in each case the amount of sodium and chloride are excreted in equimolar proportions and the change in serum osmolarity due to the electrolytes is negligible. When there is a selective excretion of sodium and a consequent lowering of the blood sodium (as after acetazolamide) there is a noticeable fall in intraocular pressure. This possibly supports the findings of Cole,[4] who has shown by precise experiments on the rabbit's eye that the influx rate of aqueous corresponds with the rate at which the sodium ions enter the eye from the plasma. The aqueous, in fact, tends to remain iso-osmotic with the plasma.—I am, etc.,

DOROTHY A. CAMPBELL.
Birmingham and Midland Eye Hospital.

REFERENCES

[1] Leydhecker, W., *Brit. J. Ophthal.*, 1950, **34**, 457.
[2] Langham, M. E., *J. Physiol. (Lond.)*, 1955, **128**, 78P.
[3] Drance, S. M., *Trans. ophthal. Soc. U.K.*, 1958, **78**, 565.
[4] Cole, D. F., *Brit. J. Ophthal.*, 1960, **44**, 225.

Bur for Skin Tests

SIR,—The usual methods of carrying out protein sensitivity tests are not very satisfactory. Intradermal injections are too delicate, and they are not easy to carry out in children. The more commonly used methods are the "scratch" and "prick" techniques. These are open to the objection that it is difficult to secure a uniform result. With the scratch method in particular, the depth of the incision may vary considerably. The result is that both of these methods lack uniformity, and the reactions often result in irregular shapes making comparison difficult.

A visit to the dentist made me speculate on the possibility of using a simple instrument which would overcome these difficulties. As we all know, the dentist uses an immense variety of small "burs"—the customary spelling in the profession. After experimenting with various sizes and shapes, I decided that the ideal for my purpose is what is termed "Ash's End-cutting Bur, No. 961." The bur can quite easily be screwed into a suitable metal handle. The skin of the forearm is held firmly and the bur is applied without any great pressure. A sharp twist leaves a small abraded area, little more than a millimetre in diameter, and it is quite easy to secure uniform depth, which need only be sufficient to remove the most superficial layers of the epidermis. The result is a row of exactly similar abrasions to which the test solutions may be applied in the usual way.

The results show greater uniformity than can be obtained by any of the other methods. The weals are circular, and they can be easily compared with the control and with the other reactions. The instrument is easy to clean after use and I have been satisfied with the improvement in results since I have been using it.—I am, etc.,

London N.W.1. JAMES MAXWELL.

Carcinoma and Cushing's Syndrome

SIR,—Dr. J. R. Billinghurst and his colleagues (August 19, p. 490) give an ample discussion on the theories concerning the interrelations of cancer and adrenal overactivity and stress the mysteriousness of this connexion. It seems that the perplexity of the problem is even more troublesome if the question is extended to malignancy in general—for instance, to the onset and spontaneous remissions of leukaemia. Clinically two facts should be taken into account. The overfunctioning adrenal cortex has at least no inhibitory property to prevent the development of tumours, and in accordance with this depressed adrenal function favours the opposite state. Guttman[1] in his large number of necropsies (566 cases) was unable to find either a leukaemic or a simultaneous malignant process outside the adrenals in Addisonian or other hypoadrenic conditions. The antimetastatic effect of adrenalectomy in tumours of the organs of secondary sexual character is explicable by the abolition of the homologous sexual hormones and has nothing to do with the above association. It seems, therefore, that the non-sexual steroids play a more important role. Pelner[2] emphasizes also the importance of those hormones which have an inhibitory action on the inflammatory defence reactions of the organism, and claims that the fewer the infectious diseases in infancy the greater will be the incidence of leukaemia (and other malignant conditions) in the adult. On this point Ungar's opinion[3] is also noteworthy: he demonstrated in his 20 years' Swiss material a low incidence of previous acute infections among cancerous patients. Forster[4] studied the incidence of neoplastic diseases among German beekeepers. He found an exceedingly low rate, 0.36 per thousand, and correlated this with the constantly stimulated immune reactions due to exposure to the toxins of bee stings. In contrast to this low incidence the Annual Statistics for 1955[5] record a tumour incidence of 1.88 in West Germany and 1.56 in Hungary per thousand living. On the other hand, Dontenwill[6] stresses the parallelism of somatic- and tumour-cell growth: both fail in the absence of adrenals. The chance of implanted tumour cells "taking" is reduced after adrenalectomy too. From these data it seems that the adrenals play a preparatory role in lessening the responses of the organism to infectious and immunological stimuli, thus allowing the progression of malignant growths, as well as directly promoting the increase of neoplasms.

Two years ago spontaneous remission of chronic myelogenous leukaemia was twice observed in a 53-year-old patient. The first instance was during cardiac failure, and as she became compensated again the leukaemia reappeared. The second, almost complete, remission occurred six months later, following a precomatic stage of her newly developing diabetes mellitus. The disturbed carbohydrate metabolism was easily restored on a carbutamide preparation and maintained on a diet containing 70 g. proteins, 150 g. carbohydrates, and 40 g. fat daily. As her blood sugar dropped to 175 mg./100 ml. from the earlier 400 mg./100 ml., the differential leucocyte count showed

the leukaemic character again. The diagnosis was confirmed at necropsy. The case has been fully reported.[7]

The congestive heart failure and the diabetic precoma both may have disturbed and lowered the function of the adrenal cortex—by the congestion due to the worsened circulation and by the exhausting effect of acidosis on the adrenals. The spontaneous remissions may be interpreted thus as signs of the adrenal hypofunction. This is in keeping with the data of Pelner's bibliographic review[2]: the majority of spontaneous remissions occurred after exhaustive infectious diseases. Moreover, the tumour-antagonistic effect of greater doses of corticosteroids can be explained by their depressive action on the patient's own hypophysial-adrenal system.

One can be in complete agreement with Dr. Billinghurst and his colleagues that no metastasis or humoral influence of the cancer is necessary to stimulate the adrenal cortex; on the contrary, it is probable that the hypercorticism enhances the malignant growth. The references and our cited case seem to confirm the opinion that the lack of adrenal function has a retarding effect on (malignant) cell proliferation.—I am, etc.,

Postgraduate Medical School, Budapest. L. MOSONYI.

REFERENCES

1. Guttman, P. H., *Arch. Path. (Chicago)*, 1930, **10**, 742 and 895.
2. Pelner, L., Fowler, G. A., and Nauts, H. C., *Acta med. scand.*, 1958, Suppl. 338.
3. Ungar, F. H., *Acta Un. int. Cancr.*, 1953, **9**, 213.
4. Forster, A. K., *Bienenzeitung (Leipzig)*, 1942, **57**, 101.
5. *Statisztikai Evkönyv*, 1959. Statiszt. Kiadó, Budapest.
6. Dontenwill, W., *Münch. med. Wschr.*, 1955, **97**, 210.
7. Mosonyi, L., *Magy. belorv. Arch.*, 1961, **14**, 97.

Neuropathy after Thalidomide ("Distaval")

SIR,—Drs. Pamela M. Fullerton and Michael Kremer (September 30, p. 855) have drawn attention to neurotoxic effects in 13 patients following treatment with thalidomide ("distaval"). They suggested the disorder was predominantly a sensory peripheral neuritis, but there was evidence of more widespread effects on the nervous system. The following psychotic disturbance in one of my patients following treatment with thalidomide may therefore be of interest.

He is a dispensing chemist, aged 47 years, who has suffered for many years from bronchial asthma, chronic bronchitis, and emphysema. There is no history, either personal or familial, of psychoses and he is virtually teetotal. He was admitted to hospital on February 22, 1961, following the sudden onset of a severe acute cardiac failure. While in hospital treatment was started with thalidomide, 50 mg. at night, in addition to the digitalis and diuretics he was already having. He responded well to treatment and was discharged on May 1 with a recommendation that this treatment be continued.

As he himself felt the sedation rather heavy, and claimed that he was susceptible to hypnotics, he cut the dose of thalidomide at first to 25 mg. and then to 12.5 mg. At the beginning of September he became depressed, lethargic, lost his appetite, and, because of insomnia (which he had never suffered from previously), increased the dose of thalidomide to 50 mg. at night. His depressive symptoms increased, and at the end of September he became agitated and for two days experienced visual and auditory hallucinations. Trees started to appear in his bedroom, the walls sloped towards the bed, the windows became smaller, and the room darker, and he was afraid something was going to fall on his head. He heard voices and answered these.

Treatment with thalidomide was stopped and within 48 hours all his hallucinations were gone. He has had no thalidomide for two weeks and is no longer depressed, his appetite has returned, and he is sleeping well with no sedation. He shows no signs of peripheral neuritis and all reflexes are present and normal.

The interesting features of this case are (1) the small dosage of thalidomide (never more than 50 mg.) taken to produce these symptoms, and (2) the apparent recovery of the patient from symptoms which both he and I thought were due wholly to worry about his underlying bronchitic condition and the uncertainty of his future business and family life. I would be interested to hear if any other practitioner has met these apparently novel symptoms in patients taking thalidomide.—I am, etc.,

Stevenston, Ayrshire. J. S. K. STEVENSON.

SIR,—We have recently investigated a patient with "thalidomide neuropathy." The lady, aged 53, had been taking 50 mg. of thalidomide nightly for 18 months. Following the oral ingestion of 100 g. of glucose, blood pyruvate and glucose levels were found almost unaltered. Faecal fat determinations over a six-day period were normal. The drug was then stopped, and a week later blood glucose levels were found to rise normally after an oral dose of 50 g. The patient agreed to restart thalidomide, and again blood glucose levels failed to rise after oral glucose. Oral D-xylose absorption and an intravenous glucose test were normal.

In this patient, therefore, thalidomide caused impairment of glucose absorption. The normal absorption of D-xylose (which is passively absorbed from the intestine) indicated that the drug interfered with the active absorption of glucose, and did not cause impaired absorption because of delayed gastric emptying.

The incidence of impaired glucose absorption in patients receiving glutarimides, the precise biochemical lesion, and its relationship to neuropathy are at present under active investigation, and we intend to publish our results at a later date.—We are, etc.,

B. W. MEADE.
S. B. ROSALKI.

Kingston Hospital Pathological Laboratory, Kingston-upon-Thames, Surrey.

SIR,—With reference to the article "Neuropathy after Intake of Thalidomide ('Distaval')" by Drs. Pamela M. Fullerton and Michael Kremer (September 30, p. 855) and Dr. L. C. F. Chevens's letter (October 14, p. 1025), I should like to describe a case in our practice.

The patient in question is 75 years of age and has taken 100 mg. "distaval" (thalidomide) nightly for the past seven months. During that period he began to complain of "pins and needles" in his fingers, burning sensations in his toes, and weakness in his legs causing interference with his walking. His palms were red but felt cold. The patient has been suffering from cramps in his calves for about 18 months (onset therefore prior to treatment with thalidomide), but these cramps became more severe during the past six months or so and started to affect the neck muscles. All neurological tests were negative.

On reading the article by Drs. Fullerton and Kremer I immediately stopped prescribing thalidomide to this patient (while watching carefully others to whom I am giving this drug). So far there has been a very slight alleviation of symptoms, but it is, of course, far too early to come to any conclusions.—I am, etc.,

Mansfield, Notts. P. K. CAHILL.

Lung Massage

SIR,—I read with great interest the article of Dr. N. F. Mistakopoulos (October 14, p. 989) on "Treatment of Experimentally Induced Bronchospasm by Air-and-Oxygen Massage of the Lungs." I feel that further experimental assessment of this method is absolutely essential before one can think of applying this method in human beings. Dr. Mistakopoulos has not provided an adequate number of controls. We are not sure of the cause of death of the one control dog. In view of its necropsy report one thinks that it might have overcome the bronchospasm before death, and it could have died of other causes like vascular shock or cardiac arrest. This would be quite understandable in view of the fact that hypotension and abnormalities of cardiac rhythm were a common feature of all the dogs during the experiments. However, I should refrain from deriving conclusions from a single poorly documented control.

If such a method ever comes in practice on human beings, it will probably be the last resort after the well-established bronchodilators have failed. Therefore, can it also be shown whether this technique of lung massage is of any value in those dogs in which bronchospasm has failed to respond to the bronchodilator drugs? From the lung-biopsy reports on Dr. Mistakopoulos's experimental dogs, I understand that there was no oedema of the bronchial walls at any stage of the bronchospasm. However, most instances of acute bronchospasms in human beings have oedema of the bronchial walls as an important feature. One would think that in this lung-massage method, by increasing the intrapleural pressure, the circulation of the lung may be embarrassed, which in turn will increase this oedema further instead of relieving it. Also, it is important to remember that if this bronchial obstruction is not fully relieved early, and if the surrounding alveoli are atelectatic, any increase of intrapleural pressure will be transmitted to these bronchial walls, thus aggravating the bronchial obstruction further.—I am, etc.,

Edinburgh. S. AHMED.

SIR,—I was very much interested in the idea of treatment of bronchospasm by air and oxygen massage of the lung, as described by Dr. N. F. Mistakopoulos (October 14, p. 989), and I appreciate the enthusiasm and spirit with which it was done. But there is one thing which is striking, and that is that the time taken in complete removal of bronchospasm was 40 to 64 minutes. Is it not possible that the effect of neostigmine might have worn off completely (we do not know the exact dose given) in 40 to 64 minutes, and, if so, then should we not consider this lung-massage another form of artificial respiration while the bronchi were under the effect of neostigmine?—I am, etc.,

Weston-super-Mare General Hospital. R. K. SRIVASTAVA.

Poliomyelitis at Hull

SIR,—In your report (October 21, p. 1091) you say, "Only two of the children (both in the 5-15 age group) have had a full course of injections of Salk vaccine." The use of the word "only" would seem inappropriate. The figures are too small to be statistically significant, but out of a total of 32 children (11 between 5 and 15) are far from reassuring. Furthermore, 12 had had one or two injections, which suggests the danger of increased susceptibility. Is the policy of vaccination during an epidemic sound?—I am, etc.,

Reigate, Surrey. T. W. PRESTON.

Anaesthesia for Tracheostomy in Children

SIR,—Having myself witnessed the tragic result of attempting to perform tracheostomy under local anaesthesia in a child of 4, I am most interested in Drs. E. H. Seward's and R. A. Fraser's description of their use of general anaesthesia (October 14, p. 987). I have no experience myself; and, having listened to Sir Robert Macintosh's remarks on the awful hazards of using general anaesthesia in cases of respiratory obstruction, I do not think I would have had the courage to attempt it.

The only suggestion I could put forward is that, from experience of other types of cases in children, I would have thought that rectal paraldehyde would have facilitated the induction and helped avoid the fear associated with any operative proceeding. From what I have myself seen, when given by a *trained* staff, rectal paraldehyde is incomparably the best premedication for children. It is safe, reliable, does not depress respiration, and does not hinder the administration of anaesthesia; indeed, it facilitates it. The atropine is of course given as well. Also, were I to be the anaesthetist, I should want the surgeon available for instant tracheostomy, which means that the paraldehyde would have to be given in the anaesthetic-room, not in the ward.

Another most interesting feature of this article is the number of cases in which ether was used. I would venture to say that many of the younger generation may not fully appreciate the value of ether when one is in a tight corner. In my own opinion, for the short case, an anaesthetic that can approach ether for safety and reliability has yet to be discovered.—I am, etc.,

Penzance, Cornwall. D. C. CLARK.

Lolly Rash?

SIR,—Semantics apart, papular urticaria, whatever its aetiology, is a dynamic condition, and lesions varying from simple erythematous patches, through papules and vesicles, to quite large bullae may be seen in the same patient. The majority of sufferers appear to halt the process at the papular stage (hence the name), but the diagnosis is not invalidated if only erythema occurs in any particular bout.

Thus the "lolly rash" described by Dr. Alun Lloyd-James (August 19, p. 525) *could* have been a *forme fruste* of papular urticaria, whatever the purists say. On the other hand, perhaps what he has been seeing is a small epidemic caused by the E.C.H.O.-9 or -16 virus, similar to the one to which I drew your attention in my letter (March 19, 1960, p. 877). Your leading article entitled "New Rashes for Old" (June 11, 1960, p. 1794) referred to this and similar outbreaks. As was pointed out at the time, the name of the condition is fifth disease or erythema infectiosum.

If this is indeed the explanation of the occurrence of this type of eruption, then the sooner we forget about the eponymous "lolly rash" the better for all concerned—including any children who may be being deprived of the favourite objects on which to satisfy their sucking

instincts, with all that that may entail on their libidos! Anyway, a diagnostic trial of feeding the correctly coloured ice-lollipops to patients who previously produced the rash would prove the point one way or another. Perhaps Dr. Lloyd-James would be willing to carry out a trial on these lines and report his findings.—I am, etc.,

Plymouth. BERNARD PECK.

Nuclear War

SIR,—On moral grounds I associate myself with the medical practitioners from Dunbartonshire (October 7, p. 964), Hammersmith Hospital (October 21, p. 1088), and elsewhere who have protested against the existence of nuclear weapons. In no circumstances could I use the bomb myself nor order its use by another. Prayers that such missiles will not be employed are not enough, nor apparently are endless conferences between leading politicians.

Doctors in all countries should write to condemn war as pathological. Its prevention comes within the scope of preventive medicine and possibly epidemiology. The words "deterrent" and "defence" convey dangerously misleading ideas. There can be no deterrent to a nuclear war arising from human accident or insanity—an increasing hazard in a world of threat and counter-threat.

As a profession we should emphasize the horrors, the psychological stupidity, and the futility of a third world war. We have cause to fear *not* death for those who are comparatively lucky but the unknown long-term effects on any survivors and on their descendants. With this background the virtues of patriotism, valour, and personal sacrifice take on a new meaning. We should foster a bolder and more rational approach to disengagement and disarmament, on the basis that the present ideological unrest is a disease, which could speedily be fatal and requires exceptional measures. Mankind either disarms or perishes.—I am, etc.,

Petts Wood, Kent. H. J. PARISH.

SIR,—It's no use sending for us then.

All waiting-rooms of G.P.s, hospitals, and clinics should have added to their present stock of posters about accidents in the home others under the above heading, setting out quite honestly the real facts and figures of an atomic war where 100 megaton bombs are used. It is high time that the lulling illusions regarding Civil Defence be exposed and every inhabitant of this island is made to realize that the only way of surviving an atomic war is to prevent one.—I am, etc.,

London W.11. ELEANOR M. ETTLINGER.

SIR,—The potential dangers of nuclear war are clear to us, and none can deny the generous sentiments of the seventeen Dunbartonshire doctors (October 7, p. 964) and those who have subsequently supported them. Each of us presumably has some form of faith or credo, and to each one of us is given the opportunity to find some practical expression to it, but I would be reluctant to give the monopoly of it to the signatories. Man is born to die. To some of us it may come mercifully and easily, like a good friend who visits us at night, to some suddenly, and to some in some painful and lingering form for a reason we shall only know when we see Him not through a glass darkly but face to face.

We have seen the results of wars, the total enslavement of bodies, and the murder of the mind, the most dreadful consequences of which we in the Western world have so far avoided by our own endeavours, and it seems to me that the signatories have not faced up to the basic problem of whether conventional weapons are justifiable for self-defence and unconventional—of whatever kind—are not. From this stems an elementary conclusion that if all are agreed that both conventional and unconventional methods should be discarded then we must go it alone without the support of our N.A.T.O. allies and our friends in the New World.

I for one do not share this view. My faith and prayers will be directed to the end that all forms of scientific endeavour will be used wisely, and my belief is that the powers of darkness will always be contained by the powers of light. In a comfortable and easy world so many of us put the thought of death away from us, and the realization that it is ever present, close to us, day by day, and week by week, may sharpen our perspectives, brighten the fires of such faith as we profess, and hasten rather than delay a working solution to the fears so naturally entertained by many of your contributors.—I am, etc.,

London S.W.1. ROBERT CUTLER.

SIR,—To protest vigorously against the manufacture, testing, and possible use of nuclear bombs can only do good, and I join my colleagues in their protest. As doctors we must also make known to the public that we can do little or nothing for those exposed to a fatal dose of radiation, unless euthanasia be called treatment. Many of us ourselves will be dead or fatally ill. The B.M.A. should ascertain, and then officially and publicly express, the attitude of our profession towards this horrible business.

But in protesting we have done nothing more than protest—we have not, for instance, made unilateral disarmament a more feasible solution to the political dilemma. If we can persuade our colleagues throughout the world to make a similar protest we may just influence the world's rulers, through their peoples, towards sanity. Our protest could help toward the development of a universal attitude of mind which would utterly reject all vile weapons of war and thus war itself. I do not see how otherwise we can help humanity, which is all of us everywhere, in this its greatest crisis.—I am, etc.,

Birmingham 20. P. H. WOODCOCK.

Research and Drug Prices

SIR,—We are told that the reason for the high price of the tetracyclines is that so much research is being done by firms which make them. Penicillin they admit has come down tremendously in price because of competition, but tetracycline must be kept high because of this research.

One would like to know which of these antibiotics has had the most research spent upon it. Surely the very many forms of penicillin that have been produced since the war by intensive and well-directed research show that there is no need for an artificially high price to produce research. I expect that the whole thing is a leg-pull.—I am, etc.,

Colchester, Essex. M. E. LAMPARD.

Oral Poliomyelitis Vaccine

SIR,—Professor G. W. A. Dick and Dr. D. S. Dane vigorously advocate (October 28, p. 1146) the continued use in this country of the Salk type of vaccine, but their letter contains arguments which can hardly pass unchallenged. They point out that the Salk vaccine we have been using is not very effective, so if we followed their advice the whole population should now be immunized again with a more potent inactivated vaccine which is not yet easily available. They ask for unequivocal evidence that the Sabin type is as safe and effective as the Salk type, but where are we to get similar evidence for the method they advocate? All methods have some uncertainties which can only be explored by years of use, so that such information can only be available for a method that has already been used for years. In spite of the good results in Sweden which they refer to, there seems to be little doubt that the Sabin type is also going to be used in that country. The reported disappearance of wild polio strains in Sweden might after all lead to a dangerous situation.

With regard to the figures for 1961 which Soloviev reported for U.S.S.R., it is surely impossible to form any conclusion from the very scanty information presented to the Oxford Conference about this year's cases, and it is quite unjustifiable to use these to suggest either lack of safety or of effectiveness.

If Professor Dick and Dr. Dane really consider oral vaccines to be potentially dangerous, it seems inconsistent for them to advocate their *gradual* introduction. The more people who have it, the less must be the risk, if there is one. Oral vaccine for all members of a family at the same time is logical and was advocated by several authorities at the Oxford meeting. In this country its maximum administration in one region at a time might be worth considering.

In 1955 many were anxious about the American programme which was followed later in this country, and to quote from a letter I wrote[1] at that time: "What will be the situation after five years as regards the millions of American children who have been given the inactivated virus?" Time has confirmed that their position is uncertain—in this country also—and, all things considered, the use of an oral attenuated virus now seems a reasonable method of strengthening the position.—I am, etc.,

United Oxford Hospitals. W. RITCHIE RUSSELL.

REFERENCE

[1] Russell, W. R., *Lancet*, 1956, **1**, 321.

The Young Pretender

SIR,—The article by Drs. K. B. Taylor and S. C. Truelove (October 7, p. 924) on the place of milk protein in the pathogenesis of ulcerative colitis suggests a diverting, if unprofitable, line of speculation on the illnesses of the Young Pretender during his Highland wanderings after the Battle of Culloden in 1746.

Prince Charles Edward was apparently not afflicted with the endemic scabies, but is said to have suffered a severe and protracted cold, nursed at Bannockburn House, that later relapsed into pneumonia. His bowels had been loose for some time and on his removal to Inverness, still febrile, were worse. Sullivan's Diary[1] contains the following observations:

"The Prince was in a terrible condition seting aside cold & hunger without even complaining, he had not a Shoe to his feet, all tore to pieces, they held only wth coards yt they tyed up wth, his toes were quit stript. . . . But as the milk did not agree with him, & yt he had no other kind of Liquor, he took a looseness, wch turned to a bloody flux. He'd not let a soul know this but old Sainclair, he grew so low & so peal yt Sullivan was frightend . . . 'if I had traicle, I'd be cured imediatly.' Sullivan remembred yt he had a little pot yt he carryed about him when he was ill himself, went imediatly & found it, the Prince took of it, with a little broath, & in three days time the flux caissed. The Prince drank no more milk, lived upon watter, & was parfectly well."

This passage is quoted by the late Sir Gordon Gordon-Taylor in his Vicary Lecture delivered on Culloden Day, 1945. He interpolates a sceptical exclamation mark after the Prince's attribution of his diarrhoea.[2] Did Bonnie Prince Charlie have ulcerative colitis? If he did, is he the first case reported with aggravation by milk? I suppose these speculations are on a level with the albinism of Noah[3] or the possible favism of Pythagoras,[4] but it would be interesting to know how the infant Pretender was suckled.—I am, etc.,

Surbiton, Surrey. P. J. E. WILSON.

REFERENCES

[1] Quoted by Taylor, A. and H., *1745 and After*, 1938. Nelson, Edinburgh.
[2] Gordon-Taylor, G., *Brit. J. Surg.*, 1945, **33**, 1.
[3] Sorsby, A., *Brit. med. J.*, 1958, **2**, 1587.
[4] Fleming, A., ibid., 1961, **1**, 1765.

Intravenous Iron

SIR,—Having read the letter of Dr. H. A. Leslie (September 16, p. 768), I am tempted to present my results with cobalt, used for augmenting the haemopoietic effect of intravenously administered saccharated iron oxide in the treatment of iron-deficiency anaemia.[1]

I gave sacoharated iron oxide ("uniferon") intravenously to one group of 16 cases, and to another comparable group of 16 cases I gave 2.5 mg. of elemental cobalt with each 100 mg. of elemental iron of saccharated iron oxide. The majority of cases were nutritional in origin. The results were controlled by the reticulocyte-count response. In the iron group the reticulocyte count reached its average peak of 11.6% on the ninth day, whereas in the iron-cobalt group the average peak of 16.8% was reached on the 13th day. The average weekly haemoglobin rise in the iron group at 7.00 to 10.99 g./100 ml. level of haemoglobin was 0.8 g./100 ml., as compared to 1.82 g./100 ml. in the iron-cobalt group. Below the 6.99 g./100 ml. level of haemoglobin it was equal in both groups. The average weekly rise in the red cell count at a level of 1.0 to 3.99 million/c.mm. was 0.54 to 0.65 million/c.mm. in the iron-cobalt group, as compared to 0.24 to 0.36 million/c.mm. in the iron group. In both the groups the treatment was commenced at least a week after hospitalization and only if the haemocytologic values showed maintenance or slight deterioration as compared to the values obtained at the time of admission. The results are sufficiently encouraging. But somehow or other cobalt is not very often used in therapy for augmenting the effect of parenteral iron. It will be interesting if other readers have any experience to offer.—I am, etc.,

Lokmanya Tilak Municipal General Hospital, Bombay 22, India. D. D. VORA.

REFERENCE

[1] Vora, D. D., *Indian J. med. Sci.*, 1956, **10**, 19.

Presentation of Glyceryl Trinitrate

SIR,—Two months ago I had an attack of acute coronary insufficiency from which I am making the customary good recovery. I had occasion to use glyceryl trinitrate tablets, *B.P.* I first tried the new white ones and found that, while they caused a headache, they had little or no effect on cardiac pain. I then secured some of the old brown chocolate trinitrins and found that even half a tablet would relieve cardiac pain.

I had found it difficult to believe when patients told me that the new trinitrins were not so effective as the old ones, but personal experience is convincing. I know that some of my patients buy the brown trinitrins for themselves and I do not blame them.

Why a chocolate content should make glyceryl trinitrate more efficacious I do not know, but wonder whether the dispersal of the active constituent accounts for it. I think in any case that there is a case for returning to the old formula.—I am, etc.,

Alverstoke, Hants. D. C. MACKENZIE.

Proposed Society of Exfoliative Cytologists

SIR,—In view of the encouraging response to our previous letter in your journal (August 12, p. 457) we would like to make it known through the same medium that a meeting has been arranged for Friday, December 1, at 6.30 p.m., in the small lecture theatre of the Royal Society of Medicine, 1 Wimpole Street, London W.1, to discuss the projected society. We very much hope that members of the medical profession interested in, and/or practising, cancer detection, endocrine cytology, or cytogenetics, etc., will be able to attend, and that they will reply to this invitation in order to give us some idea of the numbers to be expected.—We are, etc.,

M. EGERTON. F. OSMOND-CLARKE.
M. MURRAY. E. WACHTEL.

The Royal Free Hospital,
Gray's Inn Road,
London W.C.1.

POINTS FROM LETTERS

Nuclear War

Dr. R. G. MILLER (Bedford) writes: In common with your numerous correspondents, I wish to express concern about the terrible threat of nuclear war. I would not, however, wish this sentiment to be used in support of any campaign to persuade the Government of this country to renounce nuclear weapons unilaterally. Those of us who served in the last world war may recall the various courses on chemical warfare. The idea of chemical warfare was indeed repellent, but our instructors assured us that the best chance of avoiding its use lay in being prepared to defend ourselves against it and being ready to reply in kind. They may well have been right, for, in the event, poison-gas was not used on the battlefields in anger. Our protest must be against war itself, not against any particular instrument of war.

Dr. MABEL JORDAN (London N.15) writes: The B.M.A. must raise its voice and demand the dropping of all nuclear tests and manufacturing of all nuclear weapons in the world—and demand that the lead be taken by Britain. It is no good British doctors hiding behind their traditional conservatism—in this case it is *cowardice*.

Obituary

ROBERT WILLIAMSON, M.B., D.L.O., J.P.

The death of Mr. Robert Williamson on September 26 occurred with unexpected suddenness. Aged 64, he was medical superintendent and consultant ear, nose, and throat surgeon at the Newmarket General Hospital.

Robert Williamson was educated at Manchester Grammar School and served in the Royal Navy, in minesweepers and destroyers, during the first world war. Graduating M.B., Ch.B. from Manchester University in 1921, he was in general practice for a short time, but after postgraduate study in diseases of the ear, nose, and throat at Vienna he began a career in this specialty at the Beckett Hospital, Barnsley.

He settled at Withersfield, Suffolk, in 1938, after an illness, but with the outbreak of the second world war he again offered his services. His work as E.N.T. surgeon at Newmarket and Fulbourn Hospitals in the war years, and in civilian practice afterwards, was of such a high order that he became a distinguished and much respected figure over a very wide area.

His level-headed common sense and administrative ability soon involved him in much hospital committee work, which culminated in his appointment as medical superintendent at Newmarket General Hospital. There is no doubt that the evolution of this modern civilian hospital owes much to his quiet and painstaking work, and his influence will be seen and felt as long as the hospital exists.

Apart from his medical work he was exceedingly active in other spheres; indeed, few medical men are able to exert their energies in fields so wide and so diverse. Not only was he a magistrate and chairman of his Bench for many years, but he also maintained a lively interest in local government and many other public activities.

His medical colleagues and a very wide circle of friends will remember a man of quiet and kindly charm, staunchly upright, reliable, efficient, and wise. Those close to him will also remember his hearty laughter in the enjoyment of fun and in adversity his courage—courage beyond compare.

He leaves a widow, to whom he was deeply devoted.—A. W. R.

J. R. SINTON, M.D., M.R.C.P.

Dr. J. R. Sinton, consultant chest physician in the south Somerset clinical area, died at St. Bartholomew's Hospital on October 15 after a long illness. He was 44.

John Robertson Sinton was born on November 1, 1918. He had a distinguished career as a student at the London Hospital, graduating M.B., B.S. in 1944 and winning the Sir A. Clarke prize in medicine. After various house appointments he took the M.R.C.P. in 1946, proceeded M.D. in 1948, and became medical first assistant at the London. Deciding to specialize in pulmonary diseases, he was elected to a Dorothy Temple Cross travelling fellowship in tuberculosis. Having held the post of deputy physician-superintendent at Baguley Hospital, near Manchester, he moved to Somerset some years ago, and was on the staff of the general hospitals at Taunton and Yeovil.

D. V. H. writes: "Rob" Sinton spent his last, too few, years among us in Somerset as consulting chest physician. His work was first-class. Patients liked his cheerful kindly approach, and we general practitioners much appreciated his careful, accurate, and helpful letters. He did not spare himself, but worked hard despite his obvious ill-health, with many a kindly word to those much less ill than himself. He found time to be an active member of the B.M.A., being honorary secretary of the West Somerset Division for a time, and his wife gave unstinting support. He was a

well-known and respected figure at the West Somerset Medical Club, where he frequently initiated clinical discussions.

He was a most pleasant colleague, and his dry humour and kindly words of advice were always welcome. He fought his long illness with great courage and amazing cheerfulness to the end. In this he was immensely helped by the equal courage and steadfastness of his devoted wife, to whom our deep sympathy goes out. A small daughter is, as yet, too young to know what she has lost. Rob will be sorely missed by his colleagues and his patients. Many of us also keenly feel the loss of a valued personal friend.

E. F. SOOTHILL, M.Ch., F.R.C.S.

Mr. E. F. Soothill, lately senior surgical registrar at the Norfolk and Norwich Hospital, was knocked down and killed by a car just after he had landed from his ship at Melbourne on September 29. He was on his way to take up a consultant post in Sydney.

Edward Farrar Soothill was born on November 20, 1923, in Norwich, the son of the late medical officer of health of that city. Educated at the Leys School, Emmanuel College, Cambridge, and Guy's Hospital, he graduated M.B., B.Ch. in 1948. He held the post of house-surgeon at Guy's Hospital before joining the R.A.M.C. for his National Service. He was then surgical registrar in turn at the London Hospital, West Middlesex Hospital, and Guy's Hospital, before he went to Norwich in 1956 as senior registrar. He took his F.R.C.S. in 1954 and proceeded M.Ch. at Cambridge five years later. He was therefore on the threshold of a most promising career at the time of his tragic death. A scrupulously careful and skilful surgeon, he treated both patients and staff with great kindness and consideration.

He had a great love of music and was a member of the Bach Choir in London and Glasgow. Fishing and the study of wild life were among his interests, from which stemmed his love of his native Norfolk and the Highlands of Scotland. His many colleagues will greatly miss a trusted and honest friend. He led a very happy family life, and we offer our deep sympathy to his wife, three small children, and to his mother.—A. L. W.

N. R. LOCKE, M.B., Ch.B.

Dr. N. R. Locke, registrar in general medicine at the City General Hospital, Sheffield, died at his home in Newbourn, near Ipswich, on September 16 at the age of 35.

Nelson Robert Locke was born on September 24, 1925, at Bury St. Edmunds, the son of a Land Settlement Association farmer. Although receiving no secondary school education, at the age of 24 he obtained his London University matriculation by correspondence course while an agricultural worker. In 1950 he went on to study agriculture at Reading University. Stimulation of his interest in psychology and psychiatry led him to seek entrance to a medical school. In spite of financial difficulties he commenced the study of medicine at Sheffield University in 1951 and graduated M.B., Ch.B. in 1956, going on to gain the Conjoint Diploma shortly after. He will be remembered by his fellow students at Sheffield as a diligent and painstaking worker and as a man with firm Christian principles: he was an active member of the University Christian Union and for a period served as secretary to the Sheffield society.

He was house-surgeon at the Royal Infirmary, and house-physician at the City General Hospital, Sheffield. Appointed in 1957 to the post of senior house officer to the department of neurosurgery at the Royal Infirmary, Sheffield, in 1958 he served for a period as senior house officer in general medicine at the Royal Infirmary, Derby. He then took up the post of registrar in general medicine at the City General Hospital, Sheffield, in which he remained until shortly before his death. While helping in the management of general medical wards he was also actively engaged in the research work of the pulmonary function unit at the City General Hospital.

The death of Nelson Locke will mean the loss of a friend and a wise counsellor to many. With his wide interests he was somewhat of an authority on various subjects as widely differing as sports cars and classical music. His broad medical experience following on an unusually varied background made him specially suited to the study of psychiatry. Whether he was chatting with farmers in his beloved Suffolk countryside or discussing medicine with his colleagues he was always as willing to learn as he was happy to teach. In particular he will be remembered by many of the nursing profession, towards whom he showed such consideration and by whom he was held in such high regard. It was this unselfishness which inevitably meant he led a full and busy life. Whether occupied with hospital duties or with other activities he always gave of his best and will be remembered for his scrupulous attention to detail.

His true character was shown by his courage, cheerfulness, and thoughtfulness during his illness: he went to extraordinary lengths to ensure that his family and friends were not caused unnecessary distress or hardship. Sad as we are at the early passing of a friend and colleague, his unswerving Christian faith in the face of distressing disease was an object lesson to many of us. That he will be greatly missed was evident from the large attendance at the funeral service, the many wreaths that were sent, and from the many letters received by his parents. To them and to his sister we extend our deepest sympathy.—D. A. and R. P. B.

R. A. BURNETT, M.B., Ch.B.

Dr. R. A. Burnett, of Congleton, Cheshire, died suddenly on October 2 at the early age of 46.

A. J. P. writes: Ronald Andrew Burnett graduated M.B., Ch.B. at Glasgow in 1942, and after a period as an assistant medical officer in a mental institution came to Congleton during the war years as an assistant in one of the largest practices in the area, ultimately becoming the senior partner in the practice. He was of a quiet unassuming nature and greatly respected by his colleagues for his upright and strictly conscientious nature and for his work in the local Division of the B.M.A. For some years he had been secretary of the local medical committee, and his interest in this and in other B.M.A. and local hospital matters, as witnessed by his regular attendances at meetings and his shrewd common sense in discussion, will always be remembered by his fellow practitioners, and by those with whom he came into personal contact. He was a member of the general-practitioner staff of the War Memorial Hospital, Congleton, and a great favourite with staff and patients alike. We will miss him greatly in the area, and our sympathy goes out to his widow and two young children.

MABEL BREWSTER, M.R.C.S., L.R.C.P.

Dr. Mabel Brewster, who practised until recently in Willesden, died on October 10 in the Willesden General Hospital. She was 58 years of age.

Mabel Brewster was born in March, 1903, in Shirebrook, a village in Derbyshire. After finishing her education in Thornehall School, Yorkshire, she entered the Royal Free School of Medicine for Women, where she qualified in 1930. She held house posts at the Elizabeth Garrett Anderson Hospital and the Buchanan Hospital, Hastings, and then, after finishing two assistantships, she decided that general practice should be her chosen field in medicine. In 1934 she settled in Willesden, practising there until her retirement in 1960. Among other activities she was a divisional surgeon in the St. John Ambulance Brigade—during the war she was attached to the first-aid post at the Willesden General Hospital—and medical officer of an infant welfare clinic in Stepney. She also took an active part in the work of the

local Division of the B.M.A., serving on the executive committee for many years.

Mabel Brewster was a woman with a great sense of humour and of unbounding kindness. Though quick tempered, she bore no grudge, and was always fair in her judgments. She liked people, and especially children, for whom she had a Christmas tree every year at her surgery. She was much loved by her patients and colleagues alike.

After her retirement because of ill-health she bore the last year of her illness with great courage. She is survived by her father, to whom we extend our sympathy.—J. F.

W. D. CRUICKSHANK, M.B., Ch.B.

Dr. W. D. Cruickshank, who was in practice in Hinckley, Leicestershire, from 1940 to 1958, died on October 10 at Rustington, Sussex, at the age of 69.

William Durward Cruickshank was educated at Merchant Taylors School and studied medicine at the University of Aberdeen and Charing Cross Hospital, graduating M.B., Ch.B. at Aberdeen in 1915. After holding a house appointment at Charing Cross Hospital he joined the R.A.M.C. and was mentioned in dispatches for services in the Mediterranean area during the first world war. Having been demobilized with the rank of major, he returned to Charing Cross Hospital, where he first met his wife, Dr. Margaret O. Cruickshank. After their marriage in 1923 he took over the practice of her father, Dr. J. W. Meek, in South London. In 1940 he moved to Hinckley, Leicestershire, where he became medical officer of health to the Hinckley Urban District Council and Market Bosworth Rural District Council. He retired to live in Sussex in 1958.

Dr. Cruickshank is survived by his widow and two sons.

LAMBERT C. ROGERS, C.B.E., M.D., M.Ch., M.Sc. F.R.C.S., F.R.C.S.Ed., F.R.A.C.S., F.A.C.S.

The obituary of Professor Lambert Rogers was published in the *Journal* of October 21 (p. 1089).

Mr. R. D. RICHARDS writes: To your obituary of the late Professor Lambert Rogers may I, as an old student, add a personal tribute to his work as founder and first president of the Welsh Surgical Society, a virile, active, outspoken, and democratic club, comprised of surgeons from the Principality? Its affairs were most ably directed by him in its formative years, and he left an enduring tradition when some years ago, in spite of protests from its members, he resigned the presidency. Wisely, he directed the energies of the Society towards the clinical rather than the medico-political. He was always ready to listen attentively to, and comment wisely on, the communications of the most junior, when the breadth of his surgical knowledge and experience became particularly apparent. The presence of his Rolls Royce at some Welsh country hotel near the venue of each meeting was a certain sign of first-class surgical sessions, a relaxed but stimulating gathering, a dinner where we and our wives would be assured of good fellowship, and an always fresh batch of Lambert's post-prandial anecdotes.

In December, 1959, a small research unit was established in the University of Glasgow to study the provision of engineering services in hospitals (heating and ventilation, hot and cold water, energy for all forms of process work, and medical gases). Jointly sponsored by the Nuffield Provincial Hospitals Trust and the University, and financed by the former, the unit has applied itself initially to the accumulation of data bearing on the design of these engineering services in the hospital wards. It now looks forward to an extended programme of research in the period 1962–5, for which the Trust have made available a further grant of £88,500. The unit at present consists of four graduate engineers and three observers. Their investigations are carried out mainly in general hospitals in Scotland, England, and Wales.

Medical Notes in Parliament

QUESTIONS IN THE COMMONS

Mental Health Reviews

Both the Home Secretary and the Minister of Health produced before the Parliamentary session ended figures bringing up to date the reviews that have been in progress under the Mental Health Act. Mr. R. A. BUTLER informed Mr. K. ROBINSON (St. Pancras, North, Lab.) on October 23 that in the eight months from November 1, 1960, to June 30, 1961, hospital orders without restriction totalled 563, and with restriction 85. In the first category 16 patients had been admitted to the special hospitals (Broadmoor 2, Rampton 8, and Moss Side 6), and in the second category 26 (3, 21, and 2 respectively). Mr. E. POWELL told Mr. ROBINSON that up to September 30 the mental health review tribunals had considered 545 applications, and had discharged 58 patients.

Health Service Whitley Councils

The MINISTER OF HEALTH stated in answer to questions on October 23 that he had informed both sides of the Health Service Whitley Councils that the same principles would be applied to the functioning of the Health Service machinery for determining pay as were being applied in the Civil Service. "It seems to me right," he said, "that the same principles should be applied in all parts of the Government service."

Chemists' Remuneration

Mr. POWELL refused to answer, on the ground that it was hypothetical, a question by Mr. K. ROBINSON asking what action he proposed to ensure the dispensing of prescriptions in the event of chemists giving notice to terminate their contracts and withdraw from the Health Service.

Other points from Mr. Powell's replies on this subject were that he expected a saving of between £1½m. and £2m. a year from the cut in chemists' remuneration (see *Supplement*, October 28, p. 181). Following the Third Report of the Committee of Public Accounts he had arranged for a differential system of remuneration to be introduced [it came into effect this week], and had invited chemists to co-operate in a simpler inquiry into the current costs. He was considering the recommendation for differential prices in the drug tariff.

Mr. Powell also stated that he expected a saving of about £500,000 a year, before the payment of royalties, on the contract purchase of five drugs from abroad. There was no question about the quality of these articles, which were being obtained at advantageous prices.

"Lobidan"*

Mr. MARTIN LINDSAY (Solihull, C.) asked the Minister whether he was aware that a number of Health Service doctors were prescribing an anti-smoking product called "lobidan," costing £5 16s. 8d. for 120 tablets, and whether he will stop this. Mr. POWELL told Mr. Lindsay it was for the individual doctor to prescribe what drug he thought right for a particular patient; but the doctor might be called on to justify it if his prescribing costs were being investigated.

Private Nursing-homes

Mr. N. DODDS (Erith and Crayford, Lab.) asked the Minister if he had yet given consideration to the report on private nursing-homes from the National Corporation for the Care of Old People, and what action he intended. Mr. POWELL: Yes, and the problems of registering authorities have recently been discussed with the local authority associations.

---

*See "*Any Questions?*" September 2, p. 659, and "*To-day's Drugs*," February 25, p. 586. "Lobidan" contains lobeline and a mixture of rapid- and slow-acting gastric antacids.

Medico-Legal

NO APPEAL AGAINST FINDING OF INSANITY

[FROM OUR LEGAL CORRESPONDENT]

As long ago as 1915 the first Lord Reading, then Lord Chief Justice, pointed out that the state of the law was such that a defendant to a criminal charge found by a jury to be "guilty but insane" cannot appeal against that finding.[1] Such a finding is an acquittal of the accused (though he will be detained as a result of it), and the Criminal Appeal Act, 1907, did not provide for an appeal against an acquittal. Lord Reading pointed out that only the legislature could amend the law on this point. On October 9 the present Lord Chief Justice, sitting in the Court of Criminal Appeal, remarked that Lord Reading's words are still true to-day: he emphasized that it was now even more important that amending legislation should be considered (*The Times*, October 10).

The Lord Chief Justice's observations arose out of the appeal of Irene Mary Duke, who on a charge of the capital murder of William John Duke was found by the jury "guilty of manslaughter but insane, not guilty of capital murder." The verdict entered in the court record was "guilty of the act charged but insane at the time of commission." Because insanity prevents the person charged from forming any *mens rea* such a verdict is a verdict of acquittal. The present appeal was put on the basis that, although the court has no jurisdiction to hear an appeal against the finding of insanity, yet (it was submitted) it should hear an appeal against the first half of the verdict, "guilty of the act charged." The Court of Appeal held, however, that since this was not a conviction it had no jurisdiction to entertain the appeal, which was accordingly dismissed.

As the Lord Chief Justice pointed out, one result of the Homicide Act, 1957, is that some people who are in fact insane plead diminished responsibility only. There is a real conflict of practice in such a case whether the prosecution can aver that the prisoner's condition goes beyond diminished responsibility, for if the prosecution takes such a course it is in fact asking for an acquittal. If the prosecution undertakes such a course successfully the prisoner becomes liable without appeal to detention for a considerable time.

This area of the law is eminently suitable for consideration by the Criminal Law Revision Committee.

BURDEN OF PROOF IN AUTOMATISM

[FROM OUR LEGAL CORRESPONDENT]

In a recent appeal from the Court of Criminal Appeal[1] the House of Lords made some interesting observations about the burden of proof of automatism as a defence in criminal cases.

The appellant, George Bratty, aged 26, of 44 Irwin Place, Downcloney, was convicted at Downpatrick Assizes of the murder by strangulation of an 18-year-old girl. At the trial there was some evidence tendered in support of an allegation that at the time of the act the appellant was suffering from an attack of psychomotor epilepsy with the effect that he acted in a state of automatism. There was no evidence tending to show automatism from any other cause.

Three separate defences were raised at the trial. First, that the accused was not guilty because at the material time he was in a state of automatism by reason of an attack of psychomotor epilepsy; second, he was guilty only of manslaughter because his mental condition was so impaired and confused that he was incapable of forming the intent to murder; and third, that he was guilty but insane in consequence of suffering from a disease of the mind within the McNaughton rules. The disease of the mind relied on in support of the plea of insanity was psychomotor epilepsy.

[1] *R. v. Taylor* [1915] 1 Crim. App. R. 198.

What to Leave to Jury

The trial judge left the defence of insanity to the jury, and it was rejected by them, but he refused to leave the other two defences to the jury. The House of Lords held that in this particular case such a course was quite proper. Since the defence of automatism was based on the same foundation as insanity (in this case, though not necessarily in all cases), the rejection of insanity by the jury must involve the rejection of the defence of automatism. It might be that an accused would raise a defence of insanity with an alternative defence of automatism from some independent cause (e.g., sleepwalking). In those circumstances both defences would have to be put to the jury.

Their Lordships emphasized that it is necessary for a "proper foundation" to be laid by the evidence before the judge can leave the defence of automatism to the jury. The accused cannot say at the end of the prosecution's case: "The onus is on the Crown to prove beyond reasonable doubt that I am guilty; the Crown has not proved that I was not in a state of automatism and therefore I ask for an acquittal." The Lord Chancellor adopted the words of Devlin, J., in *Hill* v. *Baxter*[2]:

> It would be quite unreasonable to allow the defence to submit at the end of the prosecution's case that the Crown had not proved affirmatively and beyond a reasonable doubt that the accused was at the time of the crime sober, or not sleepwalking, or not in a trance or blackout.

Proper Direction

Once the accused has satisfied the judge that there is evidence of automatism fit for the jury to consider, the question arises: "What is the proper direction to the jury as to the degree of proof required?" The choice is between a direction that the jury will acquit if, and only if, they are satisfied on the balance of probabilities that the accused acted in a state of automatism, or a direction that they should acquit if they are left in reasonable doubt on this point. The House of Lords stated that the latter was the proper direction, even though an accused pleading insanity must prove insanity on the balance of probabilities. If the jury is left in any real doubt, on the evidence, whether an accused acted in a state of automatism, then the Crown has not proved the necessary *mens rea* (or indeed the *actus reus*) beyond reasonable doubt, and there should be an acquittal.

REFERENCES

[1] *Bratty v. Attorney-General for Northern Ireland* [1961] 3 W.L.R. 965.
[2] 1958 1 Q.B. 277.

Universities and Colleges

UNIVERSITY OF OXFORD

On November 4 the honorary degree of D.Sc. was conferred on Robert Frederick Loeb, formerly Bard Professor of Medicine in Columbia University, New York.

The Welsh Memorial Prize for 1961 has been awarded to Maria Demetrius Messinezy, Scholar of Lady Margaret Hall.

UNIVERSITY OF CAMBRIDGE

In Congregation on October 21 the following degrees were conferred:

M.B., B.CHIR.—J. B. Newth (by proxy), P. W. Harvey.
M.B.—F. B. Cookson, I. L. Mackenzie, M. H. C. Rice.

UNIVERSITY OF ST. ANDREWS

Dr. Donald Emslie-Smith has been appointed Senior Lecturer in the Department of Medicine, Queen's College, Dundee, from October 1, 1961.

UNIVERSITY OF EDINBURGH

At a meeting of the University Court held on October 23, intimation was received that Sir Derrick M. Dunlop would retire from the Christison Chair of Therapeutics at the end of the present session.

Honorary status was conferred as follows: Dr. J. C. Gould, Honorary Senior Lecturer in the Department of Bacteriology; Dr. W. M. Court Brown, Honorary Senior Lecturer in Cytogenetics; Dr. Margaret Moffat, Honorary Lecturer in the Department of Bacteriology; and Dr. W. Norman Taylor, Honorary Lecturer in the Department of Psychological Medicine.

The following appointments were announced: Dr. P. J. Abernethy and Dr. H. O. Nicholson, Demonstrators in Department of Anatomy; Mr. I. S. R. Sinclair, to the Clinical Teaching Staff, and Mr. J. W. W. Thomson, Lecturer, both in the Department of Clinical Surgery; Dr. J. Davidson, part-time Lecturer in the Department of Forensic Medicine; Dr. Joan K. Sutherland, part-time Lecturer in the General Practice Teaching Unit; Dr. G. E. Mawer, Assistant Lecturer in the Department of Materia Medica; Dr. S. H. Taylor, Senior Lecturer in the Department of Medicine; Mr. J. Chalmers, Senior Lecturer in the Department of Orthopaedic Surgery; Drs. Harold Montgomery and M. B. Smith, Lecturers in the Department of Pathology; Dr. G. H. Begbie, Senior Lecturer, and Dr. D. E. M. Taylor, Lecturer, both in the Department of Physiology; and Dr. R. J. Peters, Lecturer in the Department of Public Health and Social Medicine.

The following terminated their appointments on September 30, 1961: Dr. J. C. Gould, Senior Lecturer in the Department of Bacteriology; Mr. I. S. R. Sinclair, Senior Lecturer in the Department of Clinical Surgery; Dr. D. H. McVie, Lecturer, and Dr. I. Stokoe, part-time Lecturer, both in the General Practice Teaching Unit.

UNIVERSITY OF LONDON

The following candidates have been approved at the examinations indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN CLINICAL PATHOLOGY.—W. de C. Baker, A. J. C. Balfour, Helen V. Bashir, L. D. Berman, C. G. Berry, Betty Chu, R. V. P. Dissanayake, A. M. El Hassan, D. O. Haines, Anita M. Herdan, Maung Ko, A. O. Laja, Sheila I. Macvie, V. I. Massiah, S. T. H. H. Pilbeam, S. K. Saigol, Tan Kheng Khoo, N. E. Traub.

EXTERNAL DIPLOMA IN CLINICAL PATHOLOGY.—C. M. D. Ross, J. D. Williams.

On September 28 the degree of M.D. was awarded to D. G. Fleck.

UNIVERSITY OF WALES

The Council of the Welsh National School of Medicine has appointed Mr. Gordon Edyvean Heard Senior Lecturer in the Surgical Unit.

UNIVERSITY OF LEEDS

The honorary degree of D.Sc. was conferred on Sir Henry Dale, F.R.S., on November 7, on which date he opened the Wellcome Building at the General Infirmary at Leeds.

Mr. H. S. M. Crabb, F.D.S. R.C.S., has been appointed Professor of Conservative Dentistry in the School of Dental Surgery, as from January 1, 1962.

Mr. R. R. Macdonald, formerly Senior Registrar and Tutor, has been appointed Lecturer in the Department of Obstetrics and Gynaecology from September 1, 1961, and Mr. J. D. Atwell Lecturer in the Department of Surgery from November 1, 1961.

The title of Emeritus Professor has been conferred on Professor Digby Chamberlain on his retirement from the Chair of Clinical Surgery, and on Sir Andrew Claye on his retirement from the Chair of Obstetrics and Gynaecology.

UNIVERSITY OF SHEFFIELD

Dr. R. M. Kinsey has been appointed Assistant Medical Officer to the Student Health Service, and Dr. Patricia C. Clegg Assistant Lecturer in Physiology.

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At a quarterly comitia of the College held on October 26 the following candidates, having satisfied the Censors' Board, were elected Members of the College:

J. Anderson, M.B., J. R. Anderson, M.D., P. L. Boardman, M.B., R. Brown, M.B. E. S. Chesser, M.B., D. A. Cotton, M.B., K. Dharmadasa, M.D., A. D. Dick, M.B., R. A. Grande, M.B., J. F. Harrison, M.B., K. Horsfield, M.B., D. Hull, M.B., A. C. Ikeme, M.B., A. C. Kaeser, M.B., Major D. Kelleher, M.B., R.A.M.C., G. M. Kirk, M.B., S. Lal, M.B., P. N. Leslie, M.B., Clara Lowy, M.B., G. J. R. McHardy, B.M., F. J. C. Millard, M.B., A. Pringle, M.B., A. B. Shrank, B.M., J. L. Thirkettle, M.B., D. A. L. Watt, M.B., P. H. Wise, M.B., N. Wright, M.B.

Licences to practise were conferred upon the following 143 candidates who had passed the final examination in medicine, surgery, and midwifery of the Conjoint Board and who had complied with the by-laws of the College:

Z. Abdul-Rahman, J. I. A. Adetosoye, C. H. Amobi, Gillian E. Anderson, E. O. Archampong, Leila M. Atitulliah, Hilda Bailey, Rosemarie A. Baillod, R. N. Bale, Eva J. Banky, P. I. Banky, A. N. Barnardo, F. M. Barrett, D. M. Barrow, W. A. Befecadu Iiligu, Elzbieta M. Biel, M. F. Biggin, P. G. Bischitz, C. J. Bolt, Margaret Bray, T. G. J. Brightmore, J. K. Brown, Jill B. Brown, Helen Capron, Heather C. Chapman, J. R. A. Chawner, Rosalind E. A. Chinnock-Jones, Erpys Christopher, Barbara E. M. Clay, T. E. Cochran, Monica A. Colledge, L. J. Collier, P. E. Copus, E. S. Dadabhay, B. W. Davies, D. E. B. Davies, H. I. Davies, D. P. Dhall, D. J. Drake, Veronica A. Duffy, Diana Dutton, D. J. P. Ellis, R. H. Ellis, B. C. Elvin, F. M. Emery, M. B. Ender, Barbara A. Etheridge, Barbara D. Ford, J. M. Forsythe, Janet M. Fraser-Moodie, G. M. Frogratt, I. Gibson, M. P. Goldfinch, Susan E. Gooda, G. H. Green, J. Harris, M. K. Hee, S. L. Henry, J. A. Hersey, M. W. Hewson, V. J. M. Hickman, I. R. Hill, R. A. Hobdell, C. J. Hull, B. J. Hyde K. W. James, H. Jay, Christina M. Jenkinson, R. A. Johnson, Vanessa M. Jones, W. J. Jory, A. P. Joseph, I. Kashi, Patricia A. M. Kielty, Elizabeth M. Knott, Loretta S. W. Ko, J. M. Leigh, R. A. Lewin, Jeanette Li, C. C. P. McConnachie, J. McLauchlan, A. J. Marengo-Rowe, J. P. Matthews, A. B. Mawson, J. D. Metcalfe, B. Milroy, M. J. B. Nicholson, B. P. N. Osler, Gillian M. Ovenham, D. McC. Paterson, Krystyna B. Pawlowicz, B. J. D. Penfield, R. L. Pell, R. Phillips, Penelope J. Pollard, C. A. Porter, B. L. Prashar, B. J. Preston, R. N. W. Price, Eleanor P. Price-Jones, Patricia A. Pritchard, D. I. Prosser, T. G. Pugh, G. P. Rabey, Annette S. Raikes, D. C. Reader, P. P. Reddy, Dorothy J. Reid, J. Reuvers, D. A. Richards, Manijeh Sadr, C. N. Scott, J. G. Scott, Janina Sekler, S. L. Sellars, W. S. Shand, M. C. Shapland, G. N. Shephard P. C. Sherrington, M. A. Shirley, J. M. I. Simpson, Jill Slack, D. T. M. Smith, H. S. H. Soffer, P. G. Soutter, D. W. Straughan, B. G. Swales, J. M. Thatlewood, C. Tremlett, J. McJ. Turnbull, I. Tye, R. C. Uren, G. van der Wilk, Jennifer M. Ward, Adrianne Watkins, Sheila M. J. Webb, D. M. Welch, R. O. Weller, P. B. Wemyss-Gorman, O. C. Wetherell, K. G. D. Williams, Francis Kang Wong, N. B. Worrall.

Diplomas in Ophthalmology, in Laryngology and Otology, in Child Health, in Physical Medicine, and in Tropical Medicine and Hygiene were granted, jointly with the Royal College of Surgeons of England, to the successful candidates whose names are printed below in the report of the meetings of the Royal College of Surgeons of England held on October 12.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on October 12, with Sir Arthur Porritt, President, in the chair, a resolution of condolence was passed on the death of Professor Lambert Charles Rogers, a past member of Council and Vice-president.

The death of Professor Raffaele Bastianelli, of Rome (Honorary Fellow), was recorded with deep regret.

The admission of Mr. F. R. Moser to the Honorary Fellowship in the Faculty of Dental Surgery was reported.

The Hallett Prize was presented to Miss I. Sri Skanda Rajah, of the University of Ceylon. Handcock prizes were presented to Miss J. B. Brown, of St. Thomas's Hospital Medical School, and Dr. N. K. Coni, of Westminster Medical School.

Long-service awards and McNeill Love medals were presented to Mr. S. Wood (60 years' service), Mr. S. P. Steward (49 years' service), and Mr. J. C. Higgins (44 years' service).

The first F. R. Moser Prize of £500 for distinction in dental research was awarded to Professor A. I. Darling, F.D.S. R.C.S., M.R.C.S., L.R.C.P., of the University of Bristol.

Mr. J. B. Oldham was reappointed as representative of the College on the Court of the University of Liverpool.

Diplomas of Fellowship were granted to M. A. Ilahi and T. Coetzee.

Diplomas of Fellowship in the Faculty of Anaesthetists were granted to M. Evans and J. D. Hill, as from August 3, 1961.

Diplomas of Membership were granted to Miss J. B. Brown, A. J. Marengo-Rowe, and F. M. Barrett.

Diplomas were granted, jointly with the Royal College of Physicians of London, as follows:

DIPLOMA IN OPHTHALMOLOGY.—S. D. Adrianwala, M. K. Afridi, B. Ahmad, I. Ahmad, S. A. Ali, M. M. O. Beiram, G. H. Bevan, S. K. Biswas, J. F. Bras, Anne E. Clancy, Iswari A. Coomaraswami, J. B. Cowle, J. F. Crewdson, B. R. Dingley, M. M. S. du Toit, E. R. Earnshaw, M. Haq, Margaret M. Harkness, J. R. Hawkins, F. C. Hollows, S. N. Jebri, K. J. Kurian, S. M. Lal, G. J. B. Leslie, A. L. McKay, C. J. F. Maguire, N. S. Mangat, H. K. Mehta, M. W. Nahe, S. S. Nawgiri, G. K. Nixon, W. O. Petrie, P. W. Pitt, Dorothy M. Rees, B. A. Rodan, H. M. Rose, R. Sivagurunathan, P. Sivarajah, J. M. Small, V. H. Smith, J. T. Snow, K. G. Soni, Suzanne R. Veronneau, W. D. Waller, J. P. B. Walsh, J. Williamson, J. Winning.

DIPLOMA IN LARYNGOLOGY AND OTOLOGY.—G. Mervis, K. J. Singh.

DIPLOMA IN CHILD HEALTH.—N. K. Agarwal, Q. U. Ahmed, T. U. Ahmed, R. Anbari, Ann D. Banister, Janet I. Beggs, D. R. Benady, I. Bhatia, Sybil Birtwistle, Alice M. Bradley-Moore, M. F. H. Bush, N. Chander, Pritikana Chattopadhyay, Kim Hoe Chee, Ruth Chenoweth, Gillian A. Clarance, Jennifer P. Cruthers, L. V. Devaraian, A. H. Dossal, Julia P. Ellis, M. S. Erram, Rachel G. Evans, M. N. A. Farhat, Anne A. Ferry, I. I. Findlay, D. H. Fox, Bernadette A. Gallagher, Louise Gallagher, J. W. Gibson, Lenore Z. Gladstone, R. J. Golding, Li. S. Gunasekera, D. R. Gunraj, Elise M. Hendry, Judith M. Heron, J. A. Hill, J. D. Holiday, E. J. Housley, J. M. Howell, Rosemary A. Hunt, P. B. Jacobs, Beryl I. E. Jones, W. G. G. L. Jones, Savitri Kasemeri, Patricia A. Kent, Khin Myo Win, A. G. Krishna, V. Kumar, Patricia O. Lane, Elizabeth R. Lohoar, Mary K. Lucas, B. W. M. Macartney, R. MacLennan, Rae N. Matthews, Thein Thein Myint, B. K. H. Nair, K.

Narayan, N. E. Okoye, B. R. Pande, Saroj R. Parekh, V. R. Patel, N. C. Pegu, H. J. Phillips, S. Raiti, C. A. Ramsay, P. N. Ratan, Aileen O. B. Redmond, C. A. Reindorf, S. R. Rele, Doris E. Ribeiro, Shirley J. Richards, Jane C. H Richings, R. R. Roberts, A. Robinson, J. A. Keipert, J. R. Robinson, P. Robson, O. Serikl, M. M. Shah, D. C. Sharda, A. S. Sinnatamby, Marguerite E. Smith, J. R. Srivastava, H. Steiner, Joan Stephenson, E. P. W. Tatford, H. Teed, Sheila Thambiah, A. K. Thambiran, Dorothy E. A. Thompson, Sylvia G. Thornicroft, C. M. Tiwary, Winifred M. M. Tully, I. W. Wallace, Pamela Walton, A. F. Watson, Corinna M. Weaver, Anne G. Wesley, Mary K. West, Margaret J. Wharton, D. M. Whiteford, A. S. Wilson.

DIPLOMA IN PHYSICAL MEDICINE.—L. G. Andrews, J. F. M. Bartholomeusz, Ma Khin Kyi, Olwen V. Rees, C. D. Waltham-Weeks.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—P. Abraham, B. K. Adadevoh, A. H. A. R. Al-Mahdi, Jane E. Anwan, J. J. Arya, S. E. August-Moffatt, Myint Myint Aye, A. Banks, M. K. Bhakta, G. G. Bhure, C. Borbor, P. R. Brown, D. Bunnag, R. Carlisle, T. Chomnijarakij, W. M. Cornelius, J. L. Dhar, F. M. Dourado, D. R. Gunraj, B. K. Gupta, O. Hamid, J. R. Harrison J. G. Holmes-Smith, T. K. Jha, Evelyn M. M. Jones, Anna-Stina Jonsson, R. W. W. Kay, D. H. McFerran, Maung Tin U, T. M. Moles, A. D. Moore, O. H. E. Olsen, G. W. Peacock, S. H. Petros, O. Prakash, R. Prasad, A. Q. B. Rahman, G. Rakshit, M. P. Rele, R. G. Robinson, K. Sangsilapa, K. I. Shah, A. J. Shaw, Z.-ur-R. Siddiqi, R. C. Stewart, P. M. Stoker-Murdy, R. S. Suphanna, Donna Man-Kiu Tang, Tun Thin, S. Tjaland, Hla Tun, M. B. Watts, M. C. Wotton.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At the meeting of the Council of the College held on September 23, with the president, Mr. A. C. H. Bell, in the chair, the following were admitted to the Fellowship:

D. R. Cairns, M. H. V. Young.

The following were admitted to the Membership:

F. D. Adey, F. Akasheh, J. H. Andrew, M. Auddy, Amy P. Augustus, C. A. Barbaro, S. C. Basak, M. K. B. Mallik, R. P. Beck, V. M. Bhatt, S. K. Bhattacharjee, D. Bower, E. J. Brown, Gillian L. Browne, J. G. Bundey, A. P. Camilleri, Chun-Hian Chong, O. McK. Coltman, C. C. Curlewis, B. Das, J. J De Wet, G. H. H. Dwyer, R. P. Dyer, H. Edelstein, J. J. Eisenberg, J. H. N. Ferris, D. L. Flax, R. J. Fothergill, W. A. Fraser, S. Friedman, R. F. R. Gardner, A. G. Gordon, G. S. Hall, A. M. Hassim, G. D. Henderson, J. B. Hill, E. L. Holland, J. K. Houston, Christine M. Hyslop, J. Hughes, Florence S. Iswariah, Hilary F. Jolly, D. H. Jones, J. Kelly, H. R. Klein, Catherine M. Lamplugh, R. D. Leckie, M. R. Lee, N. N. Ling, G. Lloyd, Therese Ti-Li Lu, W. W. McDougall, J. A. McGarry, H. A. H. Melville, K. C. Mitra, S. Mukerjee, S. D. Mulye, R. N. Munday, V. S. Nawpal, B. R. Neill, D. Y. Nelson, Wendy E. Noble, E. R. Parry, N. Rahman, E. H. Ritchie, Shirley B. Robertson, Patricia G. Roose, D. K. Sarkar, Alicon V. Scott, S. P. Sen, S. K. Sen, Janet Shaw, J. Shirazi, G. O. Smith, D. B. Spanton, F. M. Spence, D. Sullivan, K. K. Swe, K. W. Tang, A. Tharmaratnam, J. Vernon-Parry, G. P. Walker, B. G. Wren, E. Yenson.

Vital Statistics

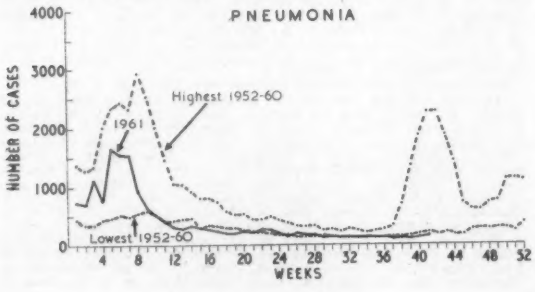
Poliomyelitis

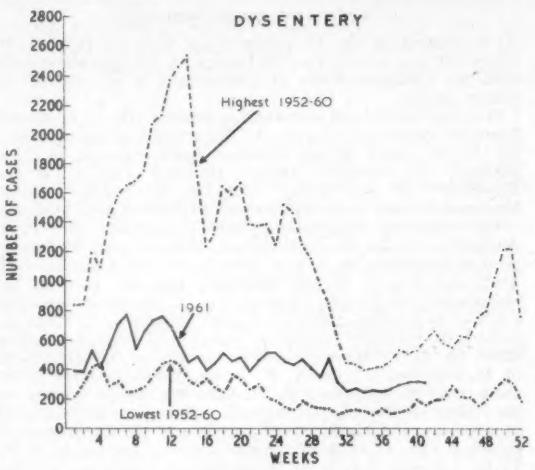
This autumn's rise in cases of poliomyelitis continued during the week ended October 21, when 94 cases (paralytic 78, non-paralytic 16) were notified. This is the highest weekly total of the year, representing an increase of 31 on the previous week and of 80 on the corresponding week last year.

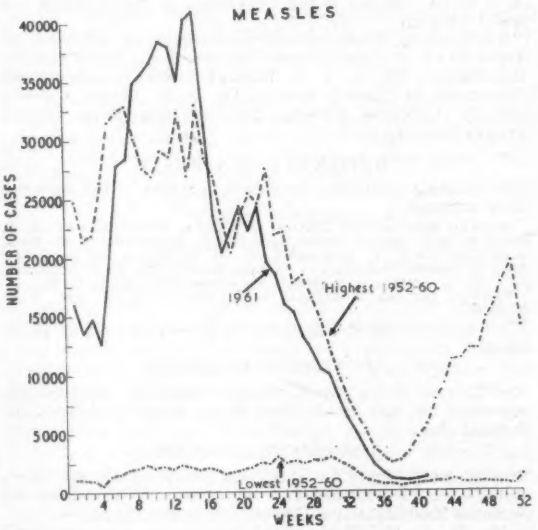
In the present outbreak of poliomyelitis in Hull the 76th case was confirmed on October 31, an increase of 9 since October 24.

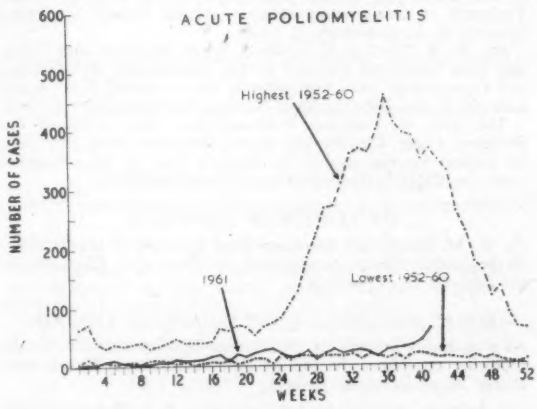
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Road Casualties in August

Of the 543 people killed on the roads of Britain in August, 176 were pedestrians, 174 were drivers or passengers in cars or other vehicles, 132 were motor-cyclists or scooter or moped riders, and 61 were pedal-cyclists. During the first eight months of the year casualties among car-drivers and

passengers showed a large increase compared with a year earlier: 961 were killed, an increase of 9%, and 13,850 were seriously injured, an increase of over 12%. Car traffic was estimated to have increased by 11% over the same period.

Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending	
Acute Poliomyelitis	Oct. 14	Oct. 21
Lancashire	17	23
Bolton C.B.	7	6
Liverpool C.B.	2	3
Oldham C.B.	1	4
Middleton M.B.	2	3
Yorkshire East Riding	29	41
Kingston upon Hull C.B.	29	40
Yorkshire West Riding	2	11
Sheffield C.B.	0	6
Dysentery		
Warwickshire	13	34
Birmingham C.B.	5	25
Glasgow	103	109
Paratyphoid Fever		
Yorkshire North Riding	1	3
Flaxton R.D.	1	3
Food Poisoning		
Cardiganshire	0	34
Aberystwyth R.D.	0	34
Monmouthshire	1	15
Tredegar U.D.	1	15
Kent	2	23
Cranbrook R.D.	0	22

Births and Deaths in Scotland

The birth rate in Scotland during the June quarter of 1961 was 19.9 per 1,000 population—0.1 above the average of the five preceding second quarters. The infant mortality was 25 per 1,000 registered live births—one below the rate for the corresponding quarter of 1960. The neonatal mortality was 18 per 1,000 live births and the stillbirths were 21 per 1,000 total births, both rates being the same as in the preceding June quarter. The death rate was 11.7 per 1,000 population, slightly above the average of the five preceding June quarters. Accidents in the home accounted for 281 deaths and motor-vehicle accidents for 176, compared with 235 and 144 respectively in the same quarter of 1960. Deaths from the principal epidemic diseases included 18 from influenza, 11 from measles, 5 from meningococcal infections, and one from whooping-cough. Deaths from respiratory tuberculosis numbered 99—13 fewer than in the corresponding quarter of 1960.

Births and Deaths in Northern Ireland

The estimated population of Northern Ireland at the middle of 1960 was 1,419,800. The birth rate in 1960 was 22.5 and the crude death rate 10.8 per thousand population. The infant mortality rate at 27 per 1,000 live births and the maternal mortality rate at 0.44 per thousand live births were the lowest ever recorded. Only 41 deaths were caused by influenza, the lowest figure for many years, and the downward trend in deaths from tuberculosis continued, the rate being 0.08 per 1,000 population. Deaths from cancer of the lung did not show any increase in 1960 over the previous year, and the rate of 0.24 per 1,000 population was only half the Scottish rate.—*Report on Health and Local Government Administration in Northern Ireland*, 1961, H.M.S.O., Belfast.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 14** (No. 41) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	1	0		4	0	0	0	
Dysentery	327	31	196	10	7	600	89	204	10	6
Encephalitis, acute	2	0		0		4	0	0	0	
Enteric fever:										
Typhoid	4	0	1	0		1	0	1	1	
Paratyphoid	10	0	4(B)	0		12	1	0	0	2
Food-poisoning	234	33	34	1		188	19	24	3	
Infective enteritis or diarrhoea under 2 years				19	25				20	28
Measles*	1,254	44	7	140	77	3,210	173	59	7	13
Meningococcal infection	15	2	6	1	1	29	2	7	0	1
Ophthalmia neonatorum	25	5	3	0		24	2	4	0	
Pneumonia†	133	5	95	0		239	15	137		
Poliomyelitis, acute:										
Paralytic	49	0	0	0	4	8	0	0	2	8
Non-paralytic	14	0	2			7	0	0		
Puerperal fever§	166	38	14	0		201	42	9	0	
Scarlet fever	336	21	24	24	10	424	28	74	27	18
Tuberculosis:										
Respiratory	332	79	72	9		426	57	72	14	
Non-respiratory	42	10	8	2		49	3	16	5	
Whooping-cough	221	16	25	14	11	933	90	91	10	29

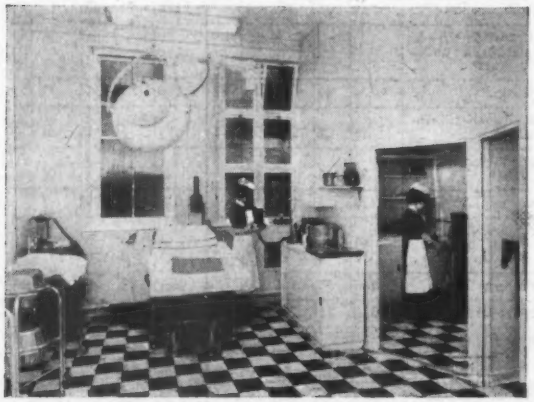
DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	2	0	2	0	0	10	2	1	0	2
Influenza	10	0	0	0	1	17	1	0	1	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	388	29	7	10	12	464	41	22	12	10
Poliomyelitis, acute	2	0		0	0	4	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	46	4	6	0	2	67	4	4	2	4
Non-respiratory		0		0	0		0	0	0	0
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	306	37	22	8	8	304	35	27	12	9
Deaths (excluding stillbirths)	8,719	687	534	105	160	9,572	757	533	113	184
LIVE BIRTHS	15,802	1347	1089	283	417	15,064	1233	1005	264	483
STILLBIRTHS	293	23	17			274	18	22		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Modernized Maternity Department

The Maternity Department at St. George's Hospital, London, has been remodelled into a much more modern and efficient working unit. Two new labour wards replace the one double-bedded labour ward. The clean and dirty areas, which were formerly combined in inadequate and cramped space, have now been incorporated in the ward, giving separate rooms accessible from either labour ward. New bathroom and toilet facilities have also been provided for the patients. There will be greater privacy for the patient during the time that she is in labour. Most of the remodelling has been carried out with the use of partitioning, and the two labour wards have been sound-proofed. Included in the alterations was the installation of a forced ventilating and air-conditioning system. The work was carried out by Holland and Hannen and Cubitts Ltd. in



One of the two new labour wards.

only eight weeks. The speed with which the work was completed was due to the use of the "parallel system" of working. In this system the contractor co-operates closely with the building owner and consultants right from the design stage. They work together as a team through to the completion of the contract, and it can go ahead much more smoothly and quickly. The board of governors has decided that in future building contracts at St. George's Hospital are to be awarded on a parallel working basis whenever suitable instead of the conventional and slower tendering system.

Chair of Bacteriology, Manchester University

Professor P. J. COLLARD, of the University College of Ibadan, Nigeria, has been appointed professor of bacteriology and director of the Department of Bacteriology in the University of Manchester. He will take up his duties in April, 1962.

Dr. Collard, who was trained at St. Bartholomew's Hospital, London, graduated in 1942. After holding an appointment as a house-physician at St. James's Hospital, Balham, he obtained his M.R.C.P.(London) in 1943. He then became R.M.O. at Hurstwood Park E.M.S. Hospital, and in 1945 became a Medical Specialist (Major) in the R.A.M.C., serving until 1948. After a period as registrar in pathology at the Westminster Hospital, in 1950 he was appointed lecturer, and subsequently senior lecturer in bacteriology at Guy's Hospital. He proceeded M.D. in 1951. He was appointed professor of bacteriology at the University College of Ibadan in the 1954 and was Dean of the Faculty of Medicine there in the year 1959–60. He is also honorary consulting bacteriologist to University College Hospital, Ibadan, and consultant adviser on industrial microbiology to the Federal Institute of Industrial Research of the Ministry of Commerce and Industry, Lagos, Nigeria. Dr. Collard's present research projects include an epidemiological survey in Northern Nigeria, measles vaccine trials, and an investigation of the biochemical lesion in the gut epithelium in shigellosis.

Hospital Costs

The weekly cost of maintaining an in-patient in N.H.S. hospitals increased on average in 1960–1 by more than 8% over the previous year. The average weekly cost in acute non-teaching hospitals was £27 13s. 6d., in London teaching hospitals £39 7s. 4d., and in provincial teaching hospitals £33 16s. The highest maintenance figure, £58 16s. per week, was at a small tuberculosis hospital with, on average, only 6 beds occupied. The weekly cost of feeding patients in acute non-teaching hospitals (£2 11s. 4d.) and in London teaching hospitals (£3 0s. 3d.) rose by rather less than 2s. on the previous year, and in provincial teaching hospitals by only 6d. The average cost of maintaining each patient for the whole of his stay rose by some 6%, which is taken to indicate that the trend towards more intensive use of beds is continuing. (Ministry of Health, *Hospital Costing Returns, Year Ended March 31, 1961*, part 1, H.M.S.O., London. Price £1 1s. net.)

Uncontaminated Processed Milk for Infants

Local authorities are to make preparations to distribute additional processed milk for infants up to 1 year old if iodine 131 in liquid milk reaches a danger level. The Health Departments propose to issue initially to each local health authority sufficient processed milk to provide each infant under 1 year old with one and a half pints of reconstituted milk a day for a fortnight. Existing welfare milk tokens would be used for the scheme. Processed milk would not be issued to expectant or nursing mothers or children over 1 except for special medical reasons.

Doctors' Window, Guildford Cathedral

About 450 doctors and many dentists, nurses, and physiotherapists were present at the Service of Dedication of Doctors', Dentists', Nurses' and Midwives', and Physiotherapists' Windows in Guildford Cathedral on October 22. Sir ARTHUR PORRITT, P.R.C.S., Acting President of the B.M.A., read the lesson and led the procession before presenting the windows to the Bishop of Guildford. The Cathedral was filled to capacity, and among the distinguished members of the medical profession in the congregation were representatives of the Royal Colleges and of the medical branches of the Armed Forces, the Master of the Society of Apothecaries, the President of the College of General Practitioners, the President of the Surrey Branch of the B.M.A., and the President of the Chartered Society of Physiotherapy. After the Service tea was provided at the Royal Surrey County Hospital by kind invitation of the matron.

Victoria Infirmary, Glasgow

A new laboratory and theatre block at the Victoria Infirmary, Glasgow, was opened last month by Mr. JOHN S. MACLAY, Secretary of State for Scotland. This building, which is the first stage of a three-phase development plan for the hospital, cost £472,000. Among the departments housed in it are the central sterile supply department and the department of medical illustration, which is believed to be the first of its kind to be planned and built as such.

Grants by Polio Research Fund

The National Fund for Research into Poliomyelitis and Other Crippling Diseases announced the following grants, totalling over £42,000. Department of Pathology, Royal Free Hospital Medical School: £15,000 for the purchase of an electron microscope. The Centre for Hip Surgery, Wrightington Hospital, Wigan: £12,000 for the erection of a clinical research department. The Public Health Laboratory Service: £5,720 for the purchase of two high-speed centrifuges for work on viruses. Virology Department, Belvidere Hospital, Glasgow: £6,600 for further research, under the direction of Dr. R. G. Sommerville, into the mode of action of synthetic antiviral compounds active against polio virus and other enteroviruses. Department of Experimental Medicine, Guy's Hospital Medical School: £1,124 for a technician to work on a study of the changes in free amino-acid patterns in human plasma, etc. Physics Depart-

ment, Guy's Hospital Medical School: £775 for a research assistant on the investigation of muscular activities in polio patients and other cases of paralysis. The Institute of Orthopaedics: £700 to investigate motor-cell distribution in the cervical spinal cord with particular reference to poliomyelitis. Department of Virology, University of Glasgow: £212 for laboratory equipment to be used in a study of the inhibition of virus infection already supported by the Fund.

Biochemical Society and "Biochemical Journal"

The office of the Biochemical Society and the editorial office of the *Biochemical Journal* will move on November 4 to 20 Park Crescent, Regent's Park, London W.1. All communications connected with the *Biochemical Journal* should be addressed to the Secretary to the Editorial Board, *Biochemical Journal*, 20 Park Crescent, Regent's Park, London W.1 (Telephone: LANgham 0888), and all other communications should be addressed to the Administrative Secretary, Biochemical Society, at the same address. (Telephone: LANgham 9849.)

In Brief

The Sir William Dunn School of Pathology at Oxford University has received the first grant made by the trustees of the Fleming Memorial Fund for Medical Research. The grant, amounting to £48,000, will be used to support electron-microscopy at the school.

COMING EVENTS

Institute of Urology.—Week-end course, "Essentials of Urology." Details are given on advertisement p. 71.

Clifford Morson Lecture, Institute of Urology.—Dr. CUTHBERT E. DUKES, "Clues to the Causes of Cancer of the Kidney," November 8, 8 p.m., Barnes Hall, Royal Society of Medicine, 1 Wimpole Street, London W.1. All medical practitioners are eligible to attend.

Bradshaw Lecture.—Professor DIGBY CHAMBERLAIN, "The Spleen and its Removal," November 9, 5 p.m., Royal College of Surgeons of England, Lincoln's Inn Fields, London W.C.2.

1st Pan-African Psychiatric Conference.—November 12–18, Aro Hospital, Abeokuta, Western Nigeria. During the conference Professor Sir AUBREY LEWIS and Sir RUSSELL BRAIN will hold clinical meetings and ward rounds at the hospital. Details from Dr. T. A. LAMBO at Aro Hospital.

University of London Heath Clark Lectures.—Course of five lectures, Professor A. V. NEALE, "Advancement of Child Health," November 13, 15, 21, 23, December 1, 5.30 p.m., London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London W.C.1. Details each week in "Societies and Lectures."

St. Thomas's Hospital.—Exhibition of documents from the hospital archives, November 14–17, 11 a.m.–6 p.m., No. 1 Lecture Theatre, St. Thomas's Hospital Medical School.

King's College Hospital Medical School, Thomas Percy Legg Memorial Lecture.—Professor Sir CHARLES ILLINGWORTH, "Clinical Applications of the Experimental Pressure Chamber," November 17, 4.30 p.m., Medical School lecture theatre, Denmark Hill, London S.E.5. Admission free, without ticket.

Skinner Lecture, Faculty of Radiologists.—Dr. FRANK ELLIS, "Bladder Neoplasms: The Challenge to the Radiotherapist," November 17, 4.30 p.m., Royal College of Surgeons, Lincoln's Inn Fields, London W.C.2. Open to all members of the medical profession without ticket.

British Society for Immunology.—Autumn meeting, November 17, 18, Wellcome Building, 183 Euston Road, London N.W.1. Programme includes symposium, "Tissue Antigens" (chairman: Dr. L. E. GLYNN). Details from Meetings' Secretary, Dr. R. G. WHITE, Bacteriology Department, The London Hospital, London E.1.

London Medical Exhibition.—November 13 (2 p.m.)–November 17, New Hall, Royal Horticultural Society, Greycoat Street, Westminster, London S.W.1. To be opened by Sir ARTHUR PORRITT, P.R.C.S., Acting President B.M.A. Details from organizers, British and Colonial Druggist, Ltd., 194–200, Bishopsgate, London E.C.2.

Royal College of Physicians of London.—Conference (primarily for Fellows and Members), "Skin Disorders in Relation to Malabsorption and Malnutrition," November 17, 2 p.m., at the College, Pall Mall East, London S.W.1. Chairman: Sir ROBERT PLATT, P.R.C.P. Parkes Weber Lecture, Dr. G. C. WELLS, "Skin Disorders in Relation to Malabsorption and Malnutrition"; Professor W. S. BULLOUGH, "Starvation, Stress, and Cell Replacement"; Professor L. J. WITTS, "Nutritional Changes in the Oral Mucosa"; Dr. M. GARRETTS, "Skin Changes in Hypocalcaemia." Details from Registrar at the College.

Faculty of Radiologists.—Postgraduate Week-end Course, November 18 and 19, the Royal College of Surgeons, Lincoln's Inn Fields, London W.C.2. Details from the Secretary of the Faculty.

13th Ciba Foundation Lecture.—Professor E. KATCHALSKI (Weizmann Institute of Science, Rehovoth), "Synthetic Macromolecules as Protein Models," November 20, 5 p.m., Royal Institute of British Architects, 66 Portland Place, London W.1. Chairman: Dr. F. H. C. Crick, F.R.S. Admission by ticket only, obtainable free from Assistant Secretary, Ciba Foundation, 41 Portland Place, London W.1 (Tel.: MUSeum 9456).

British Medical Association Lecture-Discussion.—November 23: Sir DENIS BROWNE, "Early Diagnosis of Orthopaedic Abnormalities" (chairman: Mr. H. J. SEDDON), B.M.A. House, Tavistock Square, London W.C.1, at 5.30 p.m. Tea 5 p.m. All members of Association and medical students in clinical period welcome after notifying the Secretary, British Medical Association, of proposed attendance by end of preceding week.

NEW ISSUES OF SPECIALIST JOURNALS

The Journals listed below are obtainable from the Publishing Manager B.M.A. House, Tavistock Square, London W.C.1.

BRITISH JOURNAL OF INDUSTRIAL MEDICINE

Rehabilitation: Concept and Practice. J. A. L. Vaughan Jones.
Air Pollution in Road Tunnels. R. E. Waller, B. T. Commins, and P. J. Lawther.
A Clinical Study of Electrical Accidents. W. R. Lee.
Rheumatism in Cotton Operatives. J. S. Lawrence.
Further Studies on the Toxicity of Some Tetra and Trialkyl Lead Compounds. Jill E. Cremer and S. Callaway.
A Rapid Method for the Micro-estimation of Lead in Urine. J. M. Dick, R. W. Ellis, and J. Steel.
The Distribution and Excretion of Inhaled Mercury Vapour. J. C. Gage.
The Toxicity of Precipitated Silica. P. D. Byers and J. C. Gage.
Poisoning by Ethyl Mercury Toluene Sulphonanilide. M. A. Jalili and A. H. Abbasi.
Miscellanea:
The North of England Industrial Health Advisory Service. R. C. Browne and D. Grieves.
General Assembly of the Permanent Commission and International Association on Industrial Health.
Two New Medical Centres.
Obituary.
Book Reviews.
Index to Volume 18.

Volume 18, No. 4. (Quarterly; £3 annually.)

BRITISH JOURNAL OF OPHTHALMOLOGY

Chronic Endophthalmitis Due to *Toxocara*. I. M. Duguid.
The Meibomian Glands. An Investigation into the Secretion and Some Aspects of the Physiology. R. G. Linton, D. H. Curnow, and W. J. Riley.
Dacryocystorhinostomy. An Out-patient Procedure. J. D. E. Strong.
Enzymatic Zonulolysis in Cataract Surgery. J. M. Pahwa.
Fibrous Dysplasia of the Orbital Bones. A. Mortada.
Non-central Fixation in Squinting Children. J. Scully.
Familial Glaucoma. D. G. Macpherson and K. J. Modi.
Retinopathy During Chloroquine Therapy. W. Wilson.
Degeneratio Punctata Albescens. M. A. Tadros.
Recurrent Vitreous Haemorrhage Associated with Thromboangiitis Obliterans. A. G. Cross.
Annular Peripheral Retinal Detachment Associated with Vitreous Condensation. R. Pitts Crick and J. J. Blake.
Review.
Notes.
Obituary.

Volume 45, No. 11. (Monthly; £6 annually, with *Ophthalmic Literature* and Index £9.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, November 6

CECIL GORDON MEMORIAL LECTURE.—At Anatomy Lecture Theatre, University New Buildings, Teviot Place (Doorway No. 3), Edinburgh, 5 p.m., Professor Richard Titmus: Medical Ethics and Social Change in Developing Countries.

INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—5.30 p.m., Dr. H. S. Lawrence: Delayed Allergy Homograft Sensitivity and Autoimmune Disease.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. M. A. Floyer: Possible Factors in the Mechanism of Hypertension.

Tuesday, November 7

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. H. E. Huxley, F.R.S.: Structural Aspects of Muscular Contraction.

LONDON UNIVERSITY UNION SOCIALIST SOCIETY MEDICAL GROUP.—7 p.m., Dr. D. S. Murray: Which Way the Health Service?—Welfare State and Paying Patients.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Dr. H. D. Chalke: History, Germs, and Tuberculosis.

Wednesday, November 8

CAMBRIDGE SOCIETY FOR THE STUDY OF COMPARATIVE MEDICINE.—At Addenbrooke's Hospital (Lecture Theatre of Postgraduate Medical School), Cambridge, 8 p.m., annual meeting; 8.30 p.m., Discussion on Toxoplasmosis. Openers, Dr. J. K. R. Beverley, Dr. J. W. Pawley, and Mr. W. A. Watson.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Histology—Basal Cell Epithelioma.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Professor John Crofton: Physiology of the Bronchus.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, (1) 11 a.m., discussion: Pruritus Vulvae. Guest speakers: Dr. H. J. Wallace and Professor T. N. A. Jeffcoate. (2) 3 p.m., Mr. T. N. MacGregor: Diagnosis of Sex.

INSTITUTE OF UROLOGY.—(1) At 10 Henrietta Street, London W.C., 4.30 for 5 p.m., Mr. H. G. Hanley: Male Infertility. (2) At Royal Society of Medicine (Barnes Hall), 8 p.m., Clifford Morson Lecture by Dr. Cuthbert E. Dukes: Clues to the Causes of Cancer of the Kidneys.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Hugh Owen Thomas Memorial Lecture by Professor Ivar Alvik: Treatment of the Dysplastic Hip in Childhood.

LONDON UNIVERSITY.—At School of Pharmacy, 5.30 p.m., special university lecture in physiology by Professor H. Rahn (Buffalo): (1) Adventures in Respiration—Diving, High Altitude, and Space.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. C. P. Stewart: Acid-base Metabolism in Modern Terms.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.—5.15 p.m., Professor J. C. Waterlow (Jamaica): Protein Malnutrition in Man.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. R. I. Milne: Work and Problems of a Coroner.

ROYAL SOCIETY OF HEALTH.—At Caxton Hall, Caxton Street, Westminster, S.W., 2.30 p.m., Dr. G. Stewart Prince: Prevention of Mental Illness; Dr. Catherine B. Crane: Aftercare of Mentally Disordered Patients.

Thursday, November 9

ALFRED ADLER MEDICAL SOCIETY.—At 11 Chandos Street, London W., 8 p.m., Dr. E. Weissmann: The Role of Insight in Psychotherapy.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. Joseph: Posture and Electromyography.

BROOK GENERAL HOSPITAL.—5.45 p.m., Dr. R. J. Cairns: Allergic Mechanisms and the Skin.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. K. V. Sanderson: Physiology of Hair Growth.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 11 a.m., discussion: Breast Feeding. Guest speaker: Mr. C. K. Vartan.

LIVERPOOL MEDICAL INSTITUTION.—At Adelphi Hotel, Liverpool, 7.30 p.m., annual dinner.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Bradshaw Lecture by Professor Digby Chamberlain: Spleen and its Removal.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Professor G. W. Taylor: Lymphoedema.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5.15 p.m., Professor Desmond Curran: postgraduate demonstration in psychiatry.

Friday, November 10

CLINICAL SOCIETY OF BATH.—At Teaching Department, Royal United Hospital, 8 for 8.30 p.m., symposium by Dr. D. J. Ellison, Dr. J. Cosh, Dr. R. C. Tudway, and Mr Theo Schofield: Thyroid Disease.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. J. C. Hogg: Nasal Obstruction.

LONDON UNIVERSITY.—At School of Pharmacy, 5.30 p.m., special university lecture in physiology by Professor H. Rahn (Buffalo): (2) Normal and Abnormal Ventilation-Perfusion Relationships in the Lung.

PLYMOUTH MEDICAL SOCIETY.—At North Friary House, 8.30 p.m., Mr. D. C. Bodenham: Surgical Management of Burns.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Dr. A. Crampton-Smith: Tetanus; (2) 4 p.m., Dr. N. F. Coghill: Diagnosis and Treatment of Steatorrhoea.

●ROYAL INSTITUTION.—9 p.m., Professor W. S. Bullough, D.Sc.: Modern Research on the Skin of Mice and Men.

Saturday, November 11

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, Manchester College of Science and Technology, 10.30 a.m. 410th meeting.

APPOINTMENTS

CHATTERJEE, A. K., M.B., M.R.C.P.Ed., Reader in Medicine, Medical College, Pondicherry, South India.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—R. Payne, B.M., B.Ch., D.P.M., Consultant Psychiatrist, Little Plumstead Group of Hospitals; N. A. Green, M.B., B.S., F.R.C.S., Senior Surgical Registrar, United Norwich Hospitals; B. J. Sheerin, M.B., B.S. D.A., Anaesthetic Registrar, West Suffolk General Hospital; V. S. Achar, M.B., B.S., Medical Registrar, West Norfolk and King's Lynn General Hospital; U. N. Pathak, M.B., B.S., L.M., M.M.S.A., M.R.C.O.G. D.G.O., Registrar in Obstetrics and Gynaecology, West Norfolk and King's Lynn General Hospital; L. J. de Souza, M.B., B.S., F.R.C.S.Ed., Registrar in Thoracic Surgery, Regional Thoracic Surgery Unit, Papworth Hospital; Z. Y. Al-Mallah, M.B., Ch.B., D.T.M.&H., D.T.C.D., Medical Registrar, Papworth Hospital; R. J. Schureck, M.B., B.S., Registrar in Psychiatry, Fulbourn and Addenbrooke's Hospitals; T. Izukawa, M.D., Medical Registrar, Regional Cardiac Unit, Papworth Hospital; N. P. Sen Gupta, M.B., B.S., Medical Registrar, County Hospital, Doddington; M. G. Kulkarni, M.B., B.S., D.A., Surgical Registrar, West Norfolk and King's Lynn General Hospital; E. M. Wong, M.B., Ch.B., Medical Registrar, Ipswich and East Suffolk Hospital; A. Sen Gupta, M.B., B.S., Surgical Registrar, Ipswich and East Suffolk Hospital.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London W.C.—R. A. MacMahon, M.B., B.S., F.R.C.S.Ed., Senior Surgical Registrar; A. Harrison Levy, M.B., Ch.B., F.R.C.S., Senior Surgical Thoracic Registrar; N. J. W. Royston, M.R.C.P.Ed., D.C.H., Resident Assistant Physician; T. H. Hughes-Davies, B.M., B.Ch., M.R.C.P., Senior Medical Registrar; G. Barraclough B.M., B.Ch., Registrar to Department of Morbid Anatomy; L. H. Stevens, M.B., Ch.B., M.R.A.C.P., Medical Registrar; Margaret Crump, M.B., B.S., D.A., Resident Junior Anaesthetic Registrar; J. M. Wynne, M.B., Ch.B., F.R.C.S., House-surgeon; A. G. M. Campbell M.B., Ch.B. M.R.C.P.Ed., D.C.H., and Pamela M. Zinkin, M.B., Ch.B., D.C.H., House-physicians.

MANCHESTER REGIONAL HOSPITAL BOARD.—A. Gage, M.B., Ch.B., D.P.M., Whole-time Consultant Child Psychiatrist, Local Authority Clinics at Wigan, Bolton, Rochdale, and Salford with an attachment to Booth Hall (Children's) Hospital, Manchester; R. A. Peebles Brown, M.B., B.Chir., F.R.F.P.S., M.R.C.P., Consultant Physician (nine half-days weekly), South Cheshire Group of Hospitals; P. W. Gilman, M.B., Ch.B., M.R.C.P., D.M.R.D., Whole-time Consultant Radiologist, West Manchester Group of Hospitals; N. F. Cockett, M.B., B.S., F.F.A. R.C.S., Consultant Anaesthetist (nine half-days weekly), Burnley and District Group of Hospitals; W. I. Kenyon M.B., Ch.B., M.R.C.P., Consultant Physician (eight half-days weekly), Ashton, Hyde, and Glossop Group of Hospitals; G. T. Redford, M.B., Ch.B., D.O.M.S., Consultant Ophthalmologist (seven half-days weekly), Barrow and Furness Group of Hospitals; T. D. O'Brien, M.B., B.Ch., Whole-time Assistant Physician in Geriatrics, Oldham and District Group of Hospitals; H. Thakurdas, M.B., B.S., Whole-time Assistant Psychiatrist, Prestwich Hospital; E. L. Barrett, M.B., Ch.B., Whole-time Senior Casualty Officer, Stockport and Buxton Group of Hospitals; Mary S. Medcalf, M.B., Ch.B., Whole-time Senior Casualty Officer, Westmorland County Hospital, Kendal; R. I. Keen, M.B., Ch.B., F.F.A. R.C.S., D.A., Consultant Anaesthetist (five half-days weekly), North Manchester Group of Hospitals (joint appointment with United Manchester Hospitals—four sessions); V. Rogers, M.B., Ch.B., D.M.R.D., Consultant Radiologist (nine half-days weekly), Burnley and District Group of Hospitals; J. Johnson, M.B., Ch.B., M.R.C.P.Ed., D.P.M., Consultant Psychiatrist (nine half-days weekly), Oldham and District Group of Hospitals; I. A. Harris, M.B., B.S., F.R.C.S.Ed., F.R.A.C.S., Senior Casualty Officer (whole-time), Lancaster and Kendal Group of Hospitals.

ST. GEORGE'S HOSPITAL, London S.W.—P. R. French, F.R.C.S., Consultant Surgeon to Orthopaedic Department; B. H. Pickard, M.B., B.S., F.R.C.S., D.L.O., Consultant Surgeon to Ear, Nose and Throat Department.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Walton.—On October 25, 1961, at Birmingham Maternity Hospital, to Cynthia (formerly Morris), wife of Dr. Kenneth Walton, a daughter—Susan Elizabeth.

DEATHS

Andrew.—On October 7, 1961, at Buch House, Neston, Cheshire, William Cullen Andrew, D.S.O., *M.C.*, M.B., Ch.B.

Brewster.—On October 10, 1961, Mabel Brewster, M.R.C.S., L.R.C.P., of 22 Aylestone Avenue, London N.W.

Cruickshank.—On October 10, 1961, William Durward Cruickshank, M.B., Ch.B., of 9 Hawley Road, Rustington, Sussex, aged 69.

Davidson.—On October 15, 1961, at Royal Infirmary, Dundee, Hugh Alexander Charles Davidson, L.R.C.P.&S., L.R.F.P.S., of "Fernbank," Blairgowrie, late of Conpar Angus, Perthshire.

Davis.—On October 14, 1961, in hospital, Henry Harvard Davis, *M.C.*, F.R.C.S.Ed., of Ty Dyfrig, Fairwater Road, Llandaff.

Gilmour.—On October 15, 1961, in hospital William Macmillan Gilmour, M.B., Ch.B.

Gray.—On October 7, 1961, at County Hospital, Louth, Lincs, James Gray, M.B., Ch.B., of Tetford, Lincs, aged 74.

Hadley.—On October 6, 1961, Leonard Leigh Hadley, *M.C.*, M.B., B.Ch., D.P.H., of 8 Marine Close, Worthing, Sussex.

Hutton-Ashkenny.—On October 11, 1961, at Middlesex Hospital, London W., Armly Hutton-Ashkenny, M.B., Ch.B., late of 100 Greyhound Lane, London S.W.

Macfie.—On October 6, 1961, at Aldwick End, Bognor Regis, Sussex, Thomas Hately Macfie, M.B., C.M.Ed., aged 88.

Mason.—On June 28, 1961, George William Mason, M.B., Ch.M., of "Meandetta," 2916 Pacific Hiway, Surfers Paradise, New South Wales.

Mehlmann.—On October 12, 1961, at his home 70 Sherriff Street, Rochdale, Samuel Mehlmann, Med Dr.nLwow.

Posner.—On October 8, 1961, Joseph Posner, M.R.C.S., L.R.C.P., of 174 Palatine Road, West Didsbury, Manchester.

Redmond.—On October 14, 1961, James Edward Redmond, M.B., Ch.B., aged 62.

Stanley.—On September 10, 1961, in hospital, New York, Ronald Gordon Stanley, M.B., Ch.M., of Trinidad, B.W.I.

Steadman.—On September 30, 1961, Brian St. Jermain Steadman, T.D., M.R.C.S., L.R.C.P., of 33 Wellington Square, London S.W.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Facial Hair in Pregnancy

Q.—*A patient with mild facial hirsutism has noticed the disappearance of hair during each of her pregnancies. Does this suggest the possibility that hormone therapy (e.g., progesterone) might also have some beneficial action?*

A.—The disappearance of facial hair during pregnancy must be an unusual occurrence, though the development of hirsutism in pregnancy is not uncommon. The fact that this patient has had multiple pregnancies provides prima facie evidence that endocrine function is essentially normal, so that the hirsutism is therefore presumably of constitutional origin. This being so there is no reason to suppose that hormone therapy, and certainly not progesterone, which is, in fact, slightly androgenic, would be beneficial.

Claims for Compensation for Hernia

Q.—*Can an accident such as falling, slipping, or lifting weights originate an inguinal hernia (direct or oblique) in adult workmen? By what principles are such cases judged in the courts in claims for compensation?*

A.—The question seems to imply a single strain rather than repeated strains over a long period. If a swelling in the groin appears after such an incident it usually means that there was present a pre-existing sac of congenital origin into which bowel or omentum has been forced. The hernia is therefore an oblique one which may, if untreated, subsequently increase in size. A direct hernia is less likely to be sudden in its onset and is usually due to long-continued strain acting upon weak musculature. Academically it is of course arguable that the pre-existing sac constitutes the hernia and that the entry of bowel, etc., into it is entirely secondary.

The attitude of the law has usually been the common-sense one that if it could be shown that there was no observable swelling before the incident, and there was one afterwards, then the particular strain has been held to be responsible whether or not it is recognized that a pre-existing sac was probably present. Most cases are therefore decided upon this basis although it obviously lends itself to some abuse, as when a claimant for compensation conceals the fact that he had a hernia present before the accident.

Lowering Blood Cholesterol

Q.—*When a fit man aged 48 presents a blood cholesterol of 348 mg./100 ml., a blood-pressure of 120/70, and a family history of one brother who died of coronary thrombosis at the age of 52 and a sister who had femoral thrombosis at the age of 51 and has a high blood cholesterol, to what extent is it reasonable to interfere with the patient's way of life (he is a non-smoker)?*

A.—It would seem advisable in view of the family history to attempt to reduce the patient's blood cholesterol. Reduction in total calories will effect some reduction, but nowadays it is fashionable to employ either an unsaturated-fat diet or a cholesterol inhibitor. The former can be done by substituting corn oil or maize oil for animal fat in the diet. The cholesterol inhibitor in current use is triparanol (MER-29), and this is said to lower the cholesterol independently of diet.

There is no general agreement as to the best means of dealing with a high blood cholesterol in order to avoid coronary or other arterial occlusion, and there is no certainty that reduction of blood cholesterol will play any part in preventing the complications of atherosclerosis. Indeed, once cardiac infarction has occurred there is some evidence that reduction of blood cholesterol will not prevent further complications.[1] It would seem reasonable, therefore, to see whether total calorie restriction will lower the blood cholesterol in the patient, but if not to try triparanol 250 to 500 mg. daily. An unsaturated fat diet is often difficult and sometimes unpleasant to take. Cooking with vegetable rather than animal fat may be of some assistance. If triparanol is used it should be noted that alopecia, ichthyosis, and loss of hair colour have been reported with doses over 250 mg. daily.[2] These effects will apparently reverse on discontinuing the drug or reducing the dose.

REFERENCES

[1] Oliver, M. F., and Boyd, G. S., *Lancet*, 1961, 2, 499.
[2] Achor, R. W. P., Winkelmann, R. K., and Perry, H. O., *Proc. Mayo Clin.*, 1961, 36, 217.

Can Mongols Conceive ?

Q.—*A mongol girl aged 17 who has normal periods has been sexually assaulted. Is it possible for a mongol to conceive and have children or does the chromosomal abnormality make this impossible?*

A.—Yes, it is possible for a woman who is a mongol to conceive, though this is rare. Some eight instances have been reported and four of the children resulting from the conceptions have also been mongols.[1]

REFERENCE

[1] Penrose, L. S., *Brit. med. J.*, 1961, 17, 184.

Effects of Starvation

Q.—*A healthy 30-year-old man intends to go on hunger-strike for political reasons. What permanent damage to his health is likely to result if he can keep it up for a week, and at what point will he be in danger of death from starvation?*

A.—It is assumed that the hunger striker will be drinking a limited amount of water, say 2 pints (1.1 litres) daily. In this case there will be no permanent damage to health in one week. The point at which he will be in danger of death from starvation will be governed by such factors as body build, temperament, race, climatic conditions, and exposure. Under temperate conditions no danger need be expected in a month or six weeks.

A useful guide to his condition would be a daily estimation of total urinary nitrogen output. This would be expected to fall in the second week. Thereafter any marked rise may well indicate the onset of irreversible change rapidly becoming terminal. If there is no fluid intake death may be expected after one week from dehydration and renal failure.

Lactic Acid–Peroxide Mouthwash

Q.—*What are the percentages used in lactic acid–peroxide mouthwash?*

A.—There appears to be no recognized formula for this preparation. Several modern textbooks of dental pharmacology do not include lactic acid, and reference books such as the *Extra Pharmacopoeia* (Martindale) and the *United States Dispensatory* do not mention its use as a mouthwash. Dilling and Hallam[1] state that lactic acid is a very useful caustic for oral use because of its low toxicity and that the strong acid can be applied in gingivitis and leucoplakia and to pyrrhoeal pockets and aphthous ulcers.

A formula[2] for compound lactic acid paint from the Throat Hospital pharmacopoeia contains 50% of lactic acid in glycerin with traces of formaldehyde and phenol. Another formula[3] includes lactic acid dentifrice containing 10% of lactic acid in talc flavoured with oil of peppermint. This is said to be for removing tartar from the teeth. Solutions from 0.5 to 2% are used for vaginal douches, and pessaries usually contain 5%.

Hydrogen peroxide is used as a gargle in strengths from about 1 in 10 to 1 in 4 of the *B.P.* solution (20 volumes).

Reasonable strengths for a lactic acid–hydrogen peroxide mouthwash would therefore seem to be lactic acid 2 to 10% with solution of hydrogen peroxide, *B.P.*, 10 to 25%.

REFERENCES

[1] Dilling, W. J., and Hallam, S., *Dental Materia Medica, Pharmacology and Therapeutics*, third edition, 1946, p. 112. Cassell, London.
[2] *Pharmaceutical Formulae*, 12th edition, 1953, vol. 1, p. 565. Chemist and Druggist, London.
[3] Ibid., 10th edition, 1934, vol. 2, p. 278.

NOTES AND COMMENTS

Ephedrine in Heart Block.—Dr. D. D. Ross (London S.W.3) writes: I was surprised to read the statements in "Any Questions?" (October 7, p. 971) in answer to the question about the use of ephedrine in heart block. In the reply it is stated that isoprenaline has a powerful pressor action, and is therefore of value in this condition. While most people will recognize its value in the condition it would be interesting to see the references confirming its pressor action. Ahlquist's studies[1] of adrenotropic receptors showed as early as 1948 that isoprenaline has a marked hypotensive action. Goodman and Gilman[2] state that isoprenaline brings about a marked fall in blood-pressure due to its strong peripheral vasodilatation action. One would agree with the statement that isoprenaline increases ventricular force and rate (Lands and Howard[3]) with a resultant increase in the cardiac output, but the effect on the systolic pressure is, at the best, variable, and the effect on the diastolic pressure is invariably depressant. Intravenous isoprenaline may well bring about a fall in blood-pressure so sudden and profound as to precipitate angina. I would be interested to know more recent views on this subject and if they have shown a different mode of action of isoprenaline. I also note that no mention is made of the great value of A.C.T.H. in complete heart-block.

OUR EXPERT replies: Dr. Ross is quite correct in his statements on the effects of isoprenaline on the blood-pressure, but confusion has obviously arisen between the effects in man and those in animals. The studies of Ahlquist[1] were made on dogs, cats, rats, and rabbits, and the experiments described by Lands and Howard[3] were solely concerned with animal preparations. Goodman and Gilman,[2] too, say that in the *anaesthetized animal* intramuscular or intravenous injections cause a fall in blood-pressure. It is true that they also say that the action on the systolic pressure in *man* is *variable*, with an increase in cardiac output but a fall in diastolic pressure. The answer to the question on heart block was based on personal experience in man. In considering complete heart block which occurs after intra-cardiac surgery[4] there is no question whatever but that an injection of isoprenaline causes a distinct and sometimes dramatic increase in blood-pressure. This applies mainly to the systolic pressure, and is certainly in part due to the increase in rate and increase in cardiac output. Whatever the mechanism, however, isoprenaline is a most valuable and indeed can be a life-saving drug in complete heart block in man, whatever its effects theoretically or practically may be in experimental animals or preparations. It is quite true that isoprenaline should be given with care intravenously and very small doses used. As a suppository, however, it is of great value in maintaining an adequate heart rate and blood-pressure in patients with complete heart block. No mention was made of the value of A.C.T.H. in complete heart block because the question referred to pressor amines and also because the writer has yet to be convinced of the effectiveness of A.C.T.H. in this condition.

REFERENCES

[1] Ahlquist, R. P., *Amer. J. Physiol.*, 1948, **153**, 586.
[2] Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 1955. Macmillan, New York.
[3] Lands, A. M., and Howard, J. W., *J. Pharmacol. exp. Ther.*, 1952, **106**, 65.
[4] Cleland, W. P., *et al.*, *Brit. med. J.*, 1958, **2**, 1369.

Canteen Slices.—Dr. P. A. TYSER (Cambridge) writes: In answer to the question on this subject ("Any Questions?" October 14, p. 1035) has not a further most important adverse factor been omitted? The regimen described—namely, to cook a joint, cool it, slice it, and reheat it for consumption—has been shown to favour the growth of food-poisoning organisms, with consequent dire results: this fact and that relating to loss of nutrients should, it is hoped, encourage those responsible for its perpetuation now to abandon this unfortunate practice.

Dr. J. DRUMMOND (Cambridge) writes: Has not the most important adverse effect been omitted in the answer to the question on the subject of canteen slices? Surely the danger of food-poisoning far outweighs any loss of palatability or nutritional value and would fully justify condemnation of this practice of cooling, slicing, and reheating, this being particularly true of *Clostridium welchii* infections. Of nine typical outbreaks of such food-poisoning investigated in 1959 six were caused by reheated meats and three with cold meats.[1] *Cl. welchii* is such a common contaminant of raw meat that the risk of infection is very great. As the spores survive boiling, stewing, or light roasting it is very unlikely that the large joints of meat that are used in Service catering establishments will be effectively sterilized by cooking. Slicing increases the risk of contamination and reheating is all that is necessary practically to guarantee an outbreak of food-poisoning. Such meals which may appear attractive on the menu will most certainly prove more than disappointing in the eating.

Flight-Lieutenant E. P. COLLINS (Headquarters, Coastal Command, Royal Air Force, Northwood, Middlesex) writes: With reference to your question and reply on canteen slices, while such malpractices may be seen on some stations in the Royal Air Force they are not condoned. Air Ministry policy and the teaching of the R.A.F. School of Catering both emphasize that cooking, carving, and then reheating of meat is not to take place and that meat is to be carved hot and served immediately. The other points brought out in your answer are also emphasized in a policy letter.

OUR EXPERT replies: Drs. Tyser and Drummond must be thanked for raising this important point. The answer was based on the assumption that a caterer who took the trouble to cool his meat to facilitate neat carving would either carry out the procedure promptly or at least have at his disposal adequate refrigerating space for the storage of the cooked meat. Obviously much more danger of food-poisoning would arise if the meat were stored for any length of time in the sliced condition than if the joint were stored intact and carved just before reheating. An inefficient caterer who stored sliced meat under unhygienic conditions, particularly with incomplete security against mice carrying salmonella, would indeed be running grave risks. It is satisfactory that all agree that the reheating of sliced meat is not to be recommended, even if the emphasis on the various reasons for objecting to this procedure may be different. Dr. Drummond's comments, however, might also suggest that cold meat, not reheated, is other than wholesome food. This would bring under suspicion cold beef, ham, and tongue, which are useful not only for their food value but also for the green salads which are often eaten with them. Occasional outbreaks of food-poisoning traceable to cold meats should serve as a warning for the necessity of adequate food hygiene but should not give sufficient reason to the caterer for their omission from the menu. It is gratifying to hear from Flight-Lieutenant Collins that the practice is not allowed in the R.A.F.

REFERENCE

[1] Hobbs, B. C., and Wilson, J. G., *Monthly Bull. Minist. Hlth Lab. Serv.*, 1959, **18**, 198.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Drugs in the Treatment of Disease (36s. 9d.).
Refresher Course for General Practitioners, Volume 3 (26s. 9d.).
Any Questions?, Volume 3 (8s. 3d.).

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Director, B.M.A. House, Tavistock Square, London W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the ASSOCIATION. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7 Drumsheugh Gardens, Edinburgh.